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CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

The Role of Viral Co-Infection in HIV-Associated Non-AIDS-Related Cancers

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Abstract HIV-infected individuals are at increased risk for most types of cancer, including those typically classified as non-AIDS-defining cancers (NADCs). This increased risk is likely multifactorial, but a prominent risk factor for the increased rate of some cancers is co-infection with oncogenic viruses. Anal cancer, hepatocellular carcinoma, and Hodgkin lymphoma are three of the most common NADCs, and they are associated with co-infection with human papillomavirus, hepatitis B and C, and Epstein Barr virus, respectively. This review will examine the epidemiology, pathogenesis, and future trends around these virally associated NADCs frequently found in HIV-infected individuals.

Keywords HIV · AIDS · Non-AIDS-defining cancer · Anal cancer · Hepatocellular carcinoma · Hodgkin lymphoma

Introduction

Non-AIDS-defining cancers (NADCs) are typically defined in contrast to the three AIDS-defining cancers (ADCs)—Kaposi

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sarcoma, non-Hodgkin lymphoma (NHL), and cervical cancer. NADCs are then any cancer that does not fall into the ADC category. The incidence of NADCs has been rising over the last decade as more effective antiretroviral therapy (ART) has contributed to longer life span in the HIV-infected population. Additionally, with more effective ART, the rates of ADCs have decreased, and so NADCs have supplanted ADCs as major causes of morbidity and mortality in the later ART era [1, 2]. In fact NADCs have become one of the leading causes of mortality among HIV-infected individuals in general [3, 4].

The reasons for the increased risk for NADCs are multifactorial. Factors that likely contribute to the increased risk for NADCs include HIV viremia, co-infection with oncogenic viruses, chronic immunosuppression and immune activation, exposure to high levels of carcinogens (e.g., tobacco and alcohol), aging of the HIV population, and possibly ART itself [5•, 6]. Despite being combined in the same generic category, not all NADCs share the same pathogenesis and risk factors. Recently, an effort has been made to differentiate the various NADCs based on an association with co-infecting oncogenic viruses [7•], in contrast to those NADCs that are likely infection unrelated (e.g., lung cancer or melanoma). Virally associated NADCs include anal, vaginal, vulvar, penile, and some oropharyngeal cancers (human papillomavirus (HPV)), hepatocellular cancer (hepatitis B and C), Hodgkin lymphoma (Epstein Barr virus)) and Merkel cell carcinoma (Merkel cell polyomavirus) [8]. The close association between these cancers and underlying infection with oncogenic viruses makes them much more similar to ADCs, which are all typically linked with underlying oncogenic viral infection: human herpesvirus 8 with Kaposi sarcoma, Epstein Barr Virus (EBV) with non-Hodgkin lymphoma, and HPV with cervical cancer.

Various theories have been proposed to explain the increased risk for these virally associated NADCs, including

the higher prevalence of viral co-infection in the HIV-infected population [7•], HIV-induced chronic immunosuppression permitting uncontrolled replication of the co-infecting virus, and possibly synergistic effects of HIV with the co-infecting virus. The purpose of this review is to examine the current state of knowledge for three of the most common virally associated NADCs—anal cancer, hepatocellular cancer (HCC), and Hodgkin lymphoma—and to determine what trends can be predicted based on the trajectory of the HIV epidemic.

Anal Cancer

Epidemiology

The annual incidence of anal cancer is approximately 1–2 cases per 100,000 persons globally, which is relatively low compared to the incidence of cervical cancer, which ranges from 7 cases per 100,000 in the USA [9] to 40 per 100,000 in many sub-Saharan African countries [10]. However, anal cancer is one of the most common cancers among HIV-infected individuals [11]. In a country such as the USA, the incidence of anal cancer in HIV-infected individuals is at least 30 times higher than in the general population [12, 13]. In a recent study comprised of 13 North American cohorts, anal cancer incidence was 131 in HIV-infected men who have sex with men (MSM), 46 in other HIV-infected men, and only 2 per 100,000 in HIV-uninfected men [14]. Among HIV-infected women, anal cancer incidence was 30 per 100,000, with no cases in HIV-uninfected women. In addition, anal cancer incidence continues to increase despite widespread use of highly active antiretroviral therapy (HAART) [15–17], in contrast to the observed declines in AIDS-defining cancers and other opportunistic conditions in HIV-infected individuals. One US-based study with data from 1985–2008 estimated the incidence of anal cancer in HIV-infected men to be 11 per 100,000 in the pre-HAART era, increasing to 55 per 100,000 in the post-HAART era overall, with the rate in 2006–2008 reaching 128 cases per 100,000 men [18]. Risk factors for anal cancer, in addition to HIV infection itself, include high-risk human papillomavirus (HR-HPV) infection, multiple HPV infections, high HPV viral load, receptive anal intercourse, high lifetime number of sexual partners, smoking, and older age [19]. Five-year survival after anal cancer diagnosis is quite variable by stage, cancer treatment, HAART, and CD4 count, ranging from 39–64 %, and is found to be lower than in HIV-uninfected individuals in some studies but not all [20, 21••, 22].

Pathogenesis

Anal cancer, like cervical cancer, is primarily caused by infection with high-risk oncogenic types of human papillomavirus (HR-HPV). Over 80 % of anal cancers have been attributed to HR-HPV infection, with HPV-16 the predominate type in 70 % of HPV-positive cases [23–25]. Although less is known about the natural history of anal HPV infection and its progression to cancer, it is believed to follow a course similar to the development of cervical cancer: 1) sexually transmitted HPV infects the basal layer of the squamous epithelium through micro abrasions; 2) persistent infections induce malignant transformation of the epithelial cells, which are ultimately detectable as precancerous lesions known as high-grade anal intraepithelial neoplasia (HGAIN); and 3) over time, a subset of lesions progress in the anal canal to invasive anal cancer.

Evidence suggests that HIV is a major factor in the natural history of anal cancer. Not only do HIV-infected individuals have a higher prevalence of single and multiple anal HR-HPV infections (over 90 % in some HIV-infected MSM populations [26–28]), but they are also more likely to have persistent HR-HPV infections compared to HIV-uninfected individuals [29], likely due to the weakened immune system's inability to control the infection. However, the exact relationship between CD4 count and HPV persistence and progression remains unclear. Nevertheless, HIV-infected individuals have higher incidence of anal pre-cancer and cancer as compared to HIV-uninfected individuals.

Future Directions/Trends

There are three important areas for anal cancer research and prevention. First, the role of ART, CD4 count, and HIV viral load on the natural history of anal cancer needs to be clarified. Currently, the epidemiological literature on the effect of HAART and CD4 count on the natural history of anal cancer is inconsistent and inconclusive [30, 31, 28, 32, 33, 18]. Although many support an increased risk among HIV-infected individuals with low CD4 counts, studies differ in the use or duration of ART, timing of CD4 measurement prior to cancer diagnosis, and in the examination of current versus nadir CD4 count. It is likely that the benefits that ART provides with regard to immune system recovery and reducing opportunistic conditions are outweighed by the increase in life expectancy, whereby HIV-infected individuals age into the highest risk periods for anal cancer incidence (ages 56 and 60 years in the general population for females and males, respectively [34]). The increased lifespan of HIV-infected individuals with the use of ART provides additional time for low- and high-grade precancerous lesions to progress to cancer.

Second, the performance of anal cancer screening methods needs to be improved, and clinical guidelines for screening HIV-infected individuals need to be developed and implemented. The main ways in which we can currently screen for anal pre-cancer, in order to prevent the development of

invasive anal cancer, are HPV testing, anal Pap smear, and high-resolution anoscopy (HRA). Unfortunately, each method has significant limitations, such as specificity as low as 25 % for anal HPV testing in HIV-infected MSM [35], highly variable performance of anal Pap smears across settings and populations (69–98 % for sensitivity; 69–98 % for specificity) [36], and limited availability of HRA. No randomized control trial has been conducted to compare these screening modalities. Further, treatment of precancerous lesions is quite invasive, and controversy remains regarding how and when to treat based on positive screening tests [37]. A related issue is that there are currently no consensus guidelines for screening for anal cancer in HIV-infected individuals, despite their greatly increased risk, likely due to the paucity of evidence on best screening and treatment algorithms. All of these factors likely contribute to ongoing HIV provider ambivalence about anal cancer screening [38•], which has led to nominal usage of the various techniques in the clinic. However, cost-effectiveness analyses do support routine screening in HIV-positive men and women under specific conditions and intervals [39–41].

Finally, for the maximum benefit against HPV-associated cancers for all individuals, HPV vaccine coverage needs to be increased, especially in the recommended age ranges for young boys and girls prior to sexual debut. Although there are currently no data on the effectiveness of the vaccine specifically against anal cancer in HIV-infected individuals, a study of MSM nested within a larger RCT found a 54 % reduction in anal intraepithelial neoplasia 2/3 [42] and new evidence supports the efficacy of HPV vaccination in HIV-infected individuals [43, 44]. Importantly, by vaccinating universally prior to sexually debut, when rates of HIV are much lower and before high-risk sexual behaviors such as receptive anal intercourse, we can ensure equitable and high levels of protection against HPV and anal and other associated cancers.

Hepatocellular Carcinoma

Epidemiology

HCC comprises the vast majority of primary liver cancers—accounting for over 90 % of cases. Chronic hepatitis B (HBV) and hepatitis C (HCV) are the main risk factors for development of HCC. Due to shared risk factors, the prevalence of HCV, HBV, and HIV co-infection is high. In the USA, the prevalence of HCV infection among people living with HIV ranges from 17–37 % [45, 46], while HBV co-infection is substantially lower (7 % in one large HIV cohort [47]).

As ART for HIV has reduced AIDS-related mortality, liver disease from HBV and HCV, and the NADC HCC have become more important as causes of morbidity and mortality in HIV-infected individuals [48–51, 52••]. One study found a relative risk for HCC of 3.3 (95 % CI 2.1–5.4) in HIV-infected individuals compared to the uninfected population [7•]. In one large French study, liver disease-related deaths due to HCC increased from 15 % in 2000 to 25 % in 2005 [49].

Pathogenesis

HBV can cause HCC directly; however, the majority of cases of HCC from chronic HCV infection arise from a cirrhotic liver [53]. The molecular mechanisms of virally induced HCC are still being defined. Chronic viral infection causes an ongoing cycle of inflammation, progressive hepatic fibrosis, initiation of neoplastic clones accompanied by irreversible somatic genetic/epigenetic alterations, and progression of the malignant clones in a carcinogenic tissue microenvironment [54]. The interaction between HIV and HBV with respect to the development of HCC is also less clearly established. One study found an increased risk for HCC in HBV-HIV co-infected individuals with lower CD4 cell counts [55]. A more recent study found that a greater CD4 cell count response after starting ART was associated with a decreased incidence of HCC in HBV and HCV co-infected individuals [56].

HIV infection itself has not been associated with an increased risk of HCC [57, 58]. A PubMed literature search for HIV infection and HCC yielded few studies from the USA and Europe that looked at the effect of HIV infection on the incidence, characteristics, and progression of HCC (summarized in Table 1). Most individuals in the HIV cohorts were HCV co-infected, and cumulatively, the findings of these studies support HCV as the predominant risk factor. Whereas HIV-HCV co-infection among US veterans did not increase HCC risk compared to HCV mono-infected veterans in one study [57], the risk of both cirrhosis and HCC was significantly increased among HIV-HCV co-infected veterans compared to HIV mono-infected in a second study [59]. Five of the studies compared patient and tumor characteristics between those with HIV and those without [58, 60–63]. These studies support the additive effect of HIV and HCV on risk, characteristics, and survival from HCC: reporting younger age at HCC diagnosis [60–63], more advanced disease [62, 63], faster progression from HCV diagnosis to HCC diagnosis [60, 58, 61], and worse survival [62, 63]. Accelerated development of cirrhosis among individuals with HIV-HCV co-infection compared to those with HCV mono-infection has been reported in multiple studies [64–67], but the pathogenesis of accelerated liver fibrosis that may be associated with HIV co-infection with HCV has not been established. Some suggest a role of CD4 T-cell depletion [68, 69]; however, this has not been supported by other studies that found no significant difference in CD4 counts between rapid progressors and non-rapid progressors [66, 67].

Table 1 Summary of published studies evaluating incidence of hepatocellular carcinoma in HIV-infected individuals

Reference	Year of cases	Total HIV+	Study location	Study design	Findings
García-Samaniego, 2001 [60]	1995–1999	7	Spain	Retrospective case–control series comparing seven individuals with HIV-HCV co-infection, with 31 HCV mono-infected individuals with HCC	Individuals with HIV-HCV co-infection were 1) diagnosed with HCC at younger age (median age 42 years versus 69, $P<0.001$) and 2) diagnosed with HCC at a shorter duration from HCV diagnosis (18 vs. 28 years, $P<0.05$).
Puoti, 2004 [63]	1986–2002	41	Italy and Spain	Retrospective analysis of 41 individuals with HIV and HCC, compared to two separate cohorts of HIV-negative individuals with HCC (total 1085 HIV-negative individuals)	HIV-infected individuals had the following characteristics: 1) higher prevalence of HCV co-infection, 2) more severe disease at time of HCC diagnosis, 3) significantly younger age (median 42 years vs. 65 years, $P<0.0001$) and 4) worse survival (hazard ratio, 1.63; $P=0.015$).
Giordano, 2004 [59]	1991–2000	35 with HIV and HCC	United States	Retrospective cohort study of veterans seen at Veterans Health Administration hospitals. Incidence of cirrhosis and HCC compared between 11,678 individuals with HIV only and 4761 individuals with HIV-HCV co-infection	Co-infection with HCV in individuals with HIV increased risk of cirrhosis and HCC by 10 times and 6.5 times, respectively, compared with persons with HIV only.
Kramer, 2005 [57]	1991–2000	27 with HIV and HCC	United States	Retrospective cohort of US veterans from 172 Veterans Health Administration hospitals. Incidence of cirrhosis and HCC was compared between 4761 individuals with HIV-HCV co-infection and 26,641 individuals with HCV mono-infection	In multivariate models, HIV-HCV co-infection did not predict development of HCC. Incidence of cirrhosis among veterans with HIV-HCV co-infection was lower than among veterans with HCV mono-infection. *Study did not compare patient nor tumor characteristics of HCC between HIV-HCV co-infected and HCV mono-infected.
Bräu, 2007 [61]	1992–2005	63	United States and Canada	Retrospective analysis of 63 HIV-positive individuals with HCC, compared to 226 HIV-negative individuals with HCC	Individuals with HIV have the following characteristics: 1) had a higher prevalence of HCV (71.4 versus 66.8 %) and/or HBV co-infection, 2) were younger (52 vs. 64 years, $P<0.001$), 3) were more symptomatic, 4) progressed from initial HCV diagnosis to HCC faster compared to HCV mono-infection (26 vs. 34 years, $P=0.002$), and 5) the same proportion of presentations with more advanced tumor stage as HCV mono-infection.
Bourcier, 2012 [62]	2006–ongoing	16 with HIV and primary liver cancer	France	Multicenter, prospective cohort study, comparing 16 individuals with HIV-HCV co-infection and primary liver cancer*, and 16 individuals with HCV mono-infection.	1) HIV-HCV individuals were significantly younger (48 years vs. 60 years, $P<0.001$) than HCV mono-infected individuals, 2) time intervals between viral infection and HCC diagnosis were not different between the two groups, 3) primary HCC was more advanced at diagnosis among individuals with HIV-HCV co-infection, and 4) individuals with HIV-HCV co-infection had significantly worse survival ($P=0.0005$).

Future Directions/Trends

The widespread adoption of the HBV vaccination program has contributed to an overall decrease in HCC incidence in endemic areas. A vaccination for HCV, however, remains elusive. Furthermore, with over 300 million people currently infected worldwide with HBV, secondary prevention of HCC through chronic suppression of HBV and HCV treatment remains important.

Secondary Prevention of HCC Associated with Chronic HBV and HCV Infection

As with HBV mono-infected patients, the goal of HBV treatment in HIV-HBV co-infected patients is the same: to reduce liver-related mortality outcomes. Improvement in liver fibrosis score in HIV-HBV co-infected patients with advanced fibrosis or cirrhosis receiving tenofovir has been demonstrated [70]. Piroth et al. compared the management of HBV infection in HIV-infected individuals, most of whom were on ART, compared to HIV-uninfected individuals in France [71] and found that participants with HIV were more likely to be on HBV treatment. Liver fibrosis staging did not vary significantly between the two groups. Only 3 % of patients developed HCC, with significantly lower incidence among those with HIV-HBV co-infection (0.7 vs. 4.7 %, P=0.002). In multivariate analysis, age, male gender, and cirrhosis correlated positively with HCC, whereas being HIV-infected was inversely correlated with HCC (OR 0.15, 95 % CI 0.03–0.67, P=0.01). The authors concluded that their findings suggest a decreased impact of HIV-HBV co-infection on liver-related complications such as cirrhosis and HCC and that this may be related to long-term suppression of HBV. Puoti et al. demonstrated that the use of lamivudine-containing ART in 2041 HIV-HBV co-infected patients was found to have a protective effect for liver-related deaths [72]. This study, however, did not describe how many of the liver-related deaths were due to HCC. The findings of Bruyand et al., suggesting a reduced incidence of HCC with CD4 recovery to over 500, support that a reduced incidence of HCC may be related to ART therapy with one study [73].

The treatment of HCV with attainment of sustained virologic response (SVR) has been shown to reduce all-cause and liver-related mortality and liver decompensation, although studies to date have not shown reduced incidence of HCC (when not considered as part of a composite outcome) in co-infected individuals [74–76]. The benefit of SVR on HCC incidence has been reported in HCV mono-infection [74]; however, whether this difference is due to ongoing non-HCV-mediated liver injury in HIV-infected patients or is simply a phenomenon of small numbers of SVR in HIV-HCV cohorts remains unclear. As the response to treatment for HCV has improved from interferon-based therapy to directly acting antiviral (DAA)-based regimens, with over 90 % cure

rates in clinical trials, their effect on incidence of HCV-associated HCC among HIV-infected individuals needs to be evaluated in future longitudinal studies but is expected to have a significant positive benefit.

Tertiary Prevention of HBV- and HCV-associated HCC

Relapse of HCC after initial curative treatment is high. Adjunctive antiviral therapy has been shown to be effective in reducing relapse of HBV-associated (mono-infected) HCC after curative treatment [77]. In HCV mono-infection, reduction in HCC recurrence with SVR from curative HCV treatments with interferon (IFN) has been demonstrated [78, 79], but the impact of HCV cure with DAA-based treatment on HCC outcomes has yet to be addressed. To date, there is scarce data demonstrating the efficacy of HBV or HCV antiviral treatment to prevent recurrence in patients with HIV co-infection.

Role of HCV in Non-HCC Cancers

HCV mono-infection has been associated with the development of NHL [80•, 81], a classical ADC. However, more recent literature supports an association between HCV and an increased risk for other NADCs [82]. In this study, cancer rates were nearly two times higher among HCV-infected patients after excluding liver cancers [82]. Since a significant proportion of HIV-infected patients are also HCV co-infected, HCV may be playing a role in the increased risk for some of these NADCs.

In conclusion, the field of virally induced HCC remains dynamic. The oncogenic mechanisms associated with chronic HBV and HCV continue to be elusive, and the additive role of HIV co-infection is yet to be clearly defined. The high efficacy of both HBV and current HCV treatment presents a significant opportunity to reduce the incidence and associated mortality of HCC in HIV-infected individuals.

Hodgkin Lymphoma

Epidemiology

The risk for Hodgkin lymphoma in HIV-infected individuals is substantially higher than in the general population. One meta-analysis found the risk to be 11-fold higher [83], while other studies have found standardized incidence ratios from 14.7 (95 % CI, 11.6 to 18.2) to 32.35 (95 % CI, 20.27 to 48.98) [84, 15]. One recent study analyzed the impact of HIV-infected Hodgkin lymphoma cases on the general population burden of Hodgkin lymphoma in the USA [85•]. Despite the fact that HIV-infected individuals represent only about 1 % of the general US population, Shiels et al. found that 3.8 % (848) of 22,355 Hodgkin lymphoma cases during

2000 to 2010 had HIV infection at the time of their lymphoma diagnosis. The proportion of HL cases with HIV was greater for males than females (6 vs. 1 %) and among non-Hispanic blacks (11 %) and Hispanics (7 %) compared to non-Hispanic whites (2 %).

Over the first decade of the ART era (1996–2005), the number of cases of HL in the HIV-infected population has been increasing, although the actual incidence rates have not increased [83]. Very little data have been published on HL incidence rates after 2010 in the USA or Europe.

Age

The relationship of age with HL is complicated since the incidence is bimodal or U-shaped, occurring most frequently in young and elderly adults in the general population [86]. Many NADCs have been noted to occur at younger ages in the HIV-infected population compared to the general population, although more recent analyses have shown that after adjusting for the differing age structures of the two populations, this observation is less strong. In contrast, however, individuals with AIDS were found to be significantly older than cases in the general population 42 vs. 40 years) [87]. Interestingly, in this study [87], the age distribution of AIDS individuals diagnosed with HL did not show the typical bimodal pattern seen in the general population, instead having only a single peak. The authors speculated that this difference was due to the overall lack of very young and very old individuals with AIDS in the population structure and possibly due to intermingling of the various HL subtypes in this population. A more recent study by the same group that included HIV-infected cases (not just AIDS cases) found a median age at HL diagnosis between 40 and 44 years for HIV-infected cases and between 35 and 39 years for HIV-uninfected cases [85•]. In this study, the vast majority (83 %) of cases in HIV-infected individuals were diagnosed in 30- to 59-year-olds [85•], creating a clear unimodal peak in this age range.

Timing

Recent work has examined the timing of HL diagnosis in HIV-infected individuals with respect to ART initiation. Several reports have noted an increased incidence of HL diagnosis in the first 3 to 6 months after ART initiation [88, 89, 90••], hypothesizing that there is an element of immune reconstitution inflammatory syndrome (IRIS) contributing to development of some cases. The first study was from a large French cohort of 187 HL cases among 64,368 total individuals [88]. HL risk was significantly elevated in the first 1–3 months after ART initiation (relative risk (RR) 2.95, 95 % CI 1.64 to 5.31) and was not associated with the type of ART used. A similar study from a collaboration of eight US cohorts found the incidence of HL to be nearly 2.5 times higher from 0 to 6 months after starting ART compared to the subsequent period up to

10 years [89]. Subsequent work from a prospective US lymphoma cohort extended this concept by specifying a definition of IRIS that requires the HL diagnosis within 6 months after ART initiation with reduction of viremia ≥0.5 log or full virologic suppression [90••]. This study found 15 % of HL cases met the definition for IRIS by occurring within the first 6 months after ART initiation. Cumulatively, these studies identify a substantially increased risk of HL development soon after ART initiation.

Pathogenesis

Epstein Barr Virus

One of the main differences between HIV-associated HL and HL in HIV-uninfected individuals is the strong association with EBV in the former. EBV is typically demonstrated by histopathology with latent membrane protein-1 (LMP1) in nearly all HIV-associated HL cases [91, 92]; in contrast, EBV is much less frequently (20–50 %) expressed in HL of HIV-uninfected individuals [5•]. This difference is partly due to the skewed distribution of subtypes in HIV-infected individuals, as they are more likely to have HL of mixed cellularity and lymphocyte-depleted subtypes [93, 94], which are more closely associated with EBV (see next section). LMP1 activates cellular proliferation which can promote B-cell survival and lymphomagenesis [95]. There remains some uncertainty about the interaction between EBV, the immune system, and ART in the etiologic progression to HL diagnosis, although it is generally accepted that EBV plays an etiologic role in HIV-associated HL.

Peripheral blood EBV DNA viremia has been noted to be a negative prognostic marker for survival in HIV-associated NHL [96], but the same has not been evaluated in HIV-associated HL to date. Another possible approach would be to screen for HIV-associated HL with EBV DNA viremia in certain individuals thought to be at high risk for HL or those exhibiting B symptoms. This strategy has been successful in the post-transplant setting for early detection of post-transplant lymphoproliferative disease and has not been pursued to date in HIV-associated HL but could represent a method for making earlier diagnosis possible.

Pathological Features/Subtypes

Another important difference between HIV-associated HL and HL in HIV-negative individuals is the shift in the usual proportions of the four primary HL subtypes in the former group, with a predominance of more unfavorable histological subtypes, namely lymphocyte depleted and mixed cellularity [85•, 93, 94]. In one large US-based study, the proportion of lymphocyte-depleted and mixed cellularity subtypes in the HIV cases were roughly double than that of the HIV-

uninfected cases, while the nodular sclerosis subtype was twice as frequent in HIV-uninfected cases [85•]. These two HL subtypes are more frequently associated with EBV positivity than the nodular sclerosis subtype (more common in the general population) [97•], but the etiologic reason for this shift has not been determined outside of the close relationship to EBV.

Relationship to CD4 Cell Counts

HIV-associated HL also has a complicated association with CD4 cell count. Unlike HIV-associated NHL, the risk of HL does not peak with the greatest degree of immunosuppression, i.e., the lowest CD4 counts (<50) but instead rises as CD4 increases above 50 and then declines again above 350 in an inverted U-shape. For example, a study from a large European collaboration of multiple cohorts found the highest risk for HL at a CD4 of 100–199 [98], while a large US-based study found the highest incidence in the CD4 range of 150–199 [99]. In general, the risk for HIV-associated HL has been the highest in individuals with moderate immunosuppression, a finding sharply contrasted by the progressively increased risk for NHL as immunosuppression worsens. A definitive explanation for this association has not been found, but one theory is that development of HL requires a CD4-based cellular immune response since CD4+ cells are typically found in the milieu surrounding prototypical Reed Sternberg cells [86, 100].

Epidemiologic studies of this phenomenon have also been complicated by the changing nature of CD4 cell counts prior to the diagnosis of HL in HIV-infected individuals. Frequently, peripheral CD4 cell counts decline in the months leading up to an HL diagnosis, and it is not unusual for this decrease to be a presenting sign of the developing malignancy [101]. Indeed, one large case–control study of 61 HL individuals matched to 1652 controls found during the year prior to HL diagnosis; CD4 cell counts declined by 98 cells despite suppressed HIV viremia, whereas controls gained 35 cells [98]. A second case–control study found a CD4 drop of nearly 150 cells in the year preceding HL diagnosis [102]. This finding lends further support to the necessary involvement of CD4 cells in the pathogenesis of HIV-associated HL but can complicate generalized statements about the time-updated CD4 at the time of HL diagnosis and subsequent stratification of incidence and risk. For clinicians, a falling CD4 in a virologically suppressed patient could represent a developing HL and should prompt a careful search for any signs or symptoms that could indicate an underlying malignancy.

Future Directions/Trends

Although the risk for NHL has been declining over the last decade, plus of the ART era, the incidence rates for HL have not followed. Instead, studies have generally shown a stable incidence over time with no particular protection afforded by suppressive ART [103]. With the current push for earlier initiation of ART (i.e., prior to development of AIDS) with the potential for enhanced immune control of latent EBV infection, there is a possibility that incidence rates for HIV-associated HL could begin to fall back closer to those of the general population. However, continued epidemiologic studies are needed to determine the effects of ART on incidence trends.

Conclusions

In recent years, NADCs, and particularly those associated with viral co-infections, have been dramatically increasing in incidence, and as important causes of morbidity and mortality, in HIV-infected individuals. With the current international movement toward earlier testing and treatment of all HIV-infected individuals, there is a prospect for having a significant impact on the incidence of these malignancies through earlier and better immune control. Until then, future work should concentrate on developing a better understanding of the pathogenesis of these cancers in the HIV-infected patient along with the complex interplay between the co-infecting viruses and the immune system. Improved knowledge about the biology and development of these virus-associated cancers, possible screening mechanisms, and optimal treatment options would go a long way toward improving the clinical outcomes for many individuals that are benefitting so greatly from ART.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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