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DO ANTIRETROVIRALS REDUCE THE RISK OF NON-AIDS DEFINING MALIGNANCIES?

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Abstract

Purpose of review—There is an increasing burden of non-AIDS-defining malignancies (NADM) in the antiretroviral therapy (ART) era. The recent literature is reviewed with respect to NADM risk, ART use, and immune function.

Recent findings—Recent studies have increasingly focused on individual ART use, CD4 T-cell counts and the risk of NADMs. Certain NADMs have been shown to have a reduced risk with ART use including liver, breast, colorectal, and lung cancers. NADMs associated with immunosuppression included Hodgkin's lymphoma, oral/pharynx, lung, anal, and colorectal cancers. Despite the potential protective effect of ART on some NADMs, recent studies evaluating calendar era trends have noted an increased risk of Hodgkin's lymphoma and anal cancer, and no change in risk for lung cancer in the ART era.

Summary—Successful ART use and improvements in immune function for HIV-infected persons may reduce the risk of certain NADMs. However, a continued high risk in the ART era for certain cancers have been observed, including Hodgkin's lymphoma and anal cancers. Future studies should monitor trends in NADMs in HIV-infected persons in the ART era, as well as changes in the prevalence of risk factors, co-infections, and screening practices in this population.

Keywords

HIV; antiretroviral therapy; immunodeficiency; malignancy

INTRODUCTION

Effective antiretroviral therapy (ART) use has prolonged the lifespan of HIV-infected patients and resulted in dramatic declines in the risk of AIDS clinical events, including AIDS-defining malignancies (ADM). However, there is a growing concern in the ART era for non-AIDS-defining malignancies (NADM) given the aging population of HIV-infected patients and the high prevalence of tobacco use, alcohol use and viral co-infections in this population [1]. Thus, many prior studies have focused on changes in risk in the ART era for more common NADMs in HIV patients, namely Hodgkin's lymphoma [2–6], lung [2–4,7,8], and anal [2–5,9] cancers, but with mixed results. More recent studies have evaluated malignancy risk with respect to individual ART use, including the effect of specific antiretroviral agents, ART drug classes, or ART duration. Others have evaluated the association of immune function and NADM risk which may mediate observed relationships of cancer risk and ART use.

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We provide here a summary and discussion of the recent published literature regarding malignancy risk, ART use, and immunosuppression. We performed an English-language MEDLINE search for relevant studies during the period January 2007 to July 2008.

ANTIRETROVIRAL THERAPY USE AND THE RISK OF NON-AIDS-DEFINING MALIGNANCIES

The ecologic comparison of cancer incidence before and after the introduction of ART has been the most common method for examining the effect of ART use on cancer risk [2–17]. However, this approach may not accurately reflect the association of ART on cancer incidence since other factors influencing cancer risk may have also changed over time. Furthermore, many patients may not be taking ART in the post-ART era. A few studies earlier in the ART era have examined the effect of individual ART use on cancer risk [2,17–20], although all classified ART use dichotomously as ever or never, and only Clifford et al. [2] examined individual NADMs.

Calendar-era trends

There have been substantial declines in the incidence of ADMs in the ART era [5–6,10–15]. Prior studies focusing on NADMs, however, were mixed. Higher incidence in the ART era relative to the pre-ART era have been previously demonstrated for Hodgkin's lymphoma [2, 3,6,16], non-melanoma skin [5], lung [3,7], anal [5,9], kidney [6] and for all NADMs combined [5]. Others demonstrated no calendar era changes for Hodgkin's lymphoma [4,5], non-melanoma skin [2–4], anal [2–4] all NADMs combined [2–4,6,8,17], various other individual cancers [2–6], and no change [2,4,8] or declines for lung cancer [6].

More recent studies (Table 1) with extended follow-up in the ART era support the observation of increased rates of Hodgkin's lymphoma [22**,23**] and anal cancer [22**,24*,26**], and no change in the incidence of lung cancer [22**,23**,24*,27**,28**]. Other individual cancers elevated in the ART era according to more recent studies were melanoma [22**], colorectal [22**], prostate [22**,29*], and liver [23**] cancers.

Several of these recent studies determined cancer rates by linking U.S.-based HIV/AIDS and cancer registries [23**,24*,27**]. Major strengths of registry match studies are the population-based design and the large sample sizes. However, a limitation of this study design was the inclusion of AIDS cases only, and not HIV-infected persons at earlier stages of disease. The recent cancer registry match study by Engels et. al. [23**] was notable in that both reported HIV and AIDS cases were included. Others have evaluated trends in cancer risk in cohort studies [21*,22**,25*,26**,28**,29*,30,31], which tend to be smaller in size, but include HIV patients at all stages of disease. Patel et al. [22**] reported the results of cancer risk using two large cohorts, the Adult and Adolescent Spectrum of Disease Project (n=47,832), and the HIV Outpatient Study (n=6,948). The strengths of this analysis were the large sample size, the inclusion of HIV patients with any stage of HIV/AIDS, and the ability to evaluate individual risk factors. They found higher risks of several cancers in the ART era (Table 1), but only anal cancer increased over time compared to general population rates.

Observed changes over time in risks of individual cancers may be due to differences in the prevalence of risk factors over time, or perhaps increased screening for anal, prostate or other cancers in HIV-infected patients in recent years. Few studies have evaluated cancer screening practice changes in HIV patients, although Rimland et al. [29*] noted marked increases in prostate-specific antigen testing in the ART era for HIV-infected U.S. Veterans.

Individual ART use

Studies comparing cancer rates in the pre- and post-ART era may not reflect the true effect of ART use. Thus, recent studies have increasingly focused on individual ART use and cancer risk (Table 2). In the largest study to date to evaluate the risk of cancers and individual ART use, Piketty et al. [26**] reported an increased risk for anal cancer with any ART use (hazard ratio [HR]=1.7; 95% CI=1.1–2.8), but this has not been confirmed by others [22**,24*, 37**]. Hessol et al. [24*] determined that only liver cancer among all cancers studied had a reduced risk with current ART use (HR=0.3; 95% CI=0.1–0.9), again a finding not supported by other studies [22**,35*]. Patel et al [22**] reported that any ART use was associated with a lower risk of breast (RR=0.4; p=0.013), colorectal (RR=0.5; p=0.027), and lung (RR=0.5; p<0.003) cancers. However, others have not found an association with ART use and these same cancers [24*,28**,35*]. Finally, others have reported that ART use is not associated with skin cancer [30], Hodgkin's lymphoma [22**,24*,35*], oral/pharyngeal cancers [22**,24*,35*], melanoma [22**,24*], prostate cancer [22**,24*] other various individual cancers [24*], and all NADMs combined [24*,32**,33**,35*]. Two studies by Hessol et al. [24*] and Patel et al. [22**] were unique because they reported both calendar era trends and the effect of individual ART use. Cancers associated with ART use and calendar era trends were not the same within each study, indicating that calendar era trends may reflect changes in the epidemiology of cancers, but not necessarily direct effects of individual ART use.

Individual ART medications or therapeutic classes may also have a more direct effect on cancer risk. Early studies in the ART era reported that among KS cases, lesions tended to regress after initiating a PI-based ART regimen [38–43]. Others, however, demonstrated no difference in progression of KS [44,45] or NHL [46] comparing PI-based and PI-sparing regimens. Only one cohort study to date has evaluated individual PIs, namely nelfinavir and indinavir, on any NADM risk and found no association [34**]. Experimentally, a beneficial effect for PIs has been demonstrated for KS [47–49], and for ritonavir [50], saquinavir [50,51], indinavir [50], nelfinavir [52–55] and atazanavir [54] in human cancer cells. Phase I clinical trials are underway to evaluate nelfinavir as a potential anti-cancer agent [56]. As demonstrated for KS [49], it is possible that PIs may have an indirect effect through improved immune surveillance for cancer cells or a direct effect on the development of cancer. The proposed mechanism of nelfinavir was the induction of endoplasmic reticulum stress and resulting cell death [52–54].

An additional concern regarding cancer risk and antiretroviral use is the recent introduction and use of newer ART classes such as entry, fusion, and integrase inhibitors. It is biologically feasible, for example, that inhibition of these mechanisms may interfere with tumor surveillance. Early trial results suggested the possibility of a higher risk of malignancies in raltegravir-treated [36] or vicriviroc-treated [57] patients versus placebo, while others have shown no increased malignancy risk for maraviroc-treated patients [58,59]. Ongoing surveillance for malignancies is needed for these therapies given the limited use in HIV-infected populations to date.

IMMUNODEFICIENCY AND RISK OF CANCER

As described, the decreased incidence for certain NADMs in the ART era may be a result of better immune surveillance for malignancy. Prior studies have indicated that individual NADMs associated with immunodeficiency include Hodgkin's lymphoma [2,60–62], lung [60], penile [60], lip [60], testicular [60,61], sarcomas [60,61,63], myeloma [61], and brain [61], but others have not found this association with NADMs [8,17,64–66]. Many prior studies relied on proximity to the AIDS diagnosis as a marker for immunodeficiency [60,61–63,67], with few examining the association of CD4 T-cell counts and NADM risk [2,64].

AIDS diagnosis

Several recent studies have also reported on the association of a prior AIDS diagnosis [23**, 26**,27**,68**] and the risk of NADMs (Table 3). Cancers shown to be elevated following a diagnosis of AIDS include Hodgkin's lymphoma [23**], oral/pharynx [23**], lung [23**, 27**], and anal [26**] cancers. In addition, in a large cohort of HIV-infected persons with known dates of seroconversion in EUROSIDA, Marin et al. [68**] reported higher rates of fatal NADM for those with a diagnosis of AIDS. However, a diagnosis of AIDS likely provides a poor indication of the current immune status for HIV-infected persons, particularly with the substantial improvements observed under ART, including those with a prior AIDS diagnosis.

CD4 T-cell counts

Many recent studies have evaluated the relationship of NADM risk and CD4 T-cell counts, a more direct measure of immune function (Table 3). Two recent cancer registry match studies incorporated CD4 T-cell counts [23**,27**]. Engels et al. [23**] reported no association of CD4 T-cell counts at HIV registration and risk of any individual NADM, and Chaturvedi et al. [27**] reported no association of CD4 T-cell counts at AIDS registration and risk of lung cancers. Cohort studies and RCTs, although generally smaller in size, have evaluated other measures of immune status, including baseline (i.e. study entry) [71**], current [69*,70*], nadir CD4 T-cell counts [22**,26**,28**,32**,37**,68**], and duration of low CD4 T-cell counts [33**]. In a large cohort study among U.S. Veterans, Bedimo et al. [71**] determined that CD4 T-cell counts at baseline were lower for those with anal cancer, Hodgkin's lymphoma, and any NADM combined compared to those without these cancers. The association of current CD4 T-cell counts and NADM risk was evaluated in FIRST [69*] and D:A:D [70*]. In FIRST [69*], the authors reported an HR for any NADM of 0.82 (95% CI=0.68, 0.98) per 100 cells/uL higher. In D:A:D, the authors reported an RR for fatal NADMs of 0.61 (95% CI=0.57, 0.66) per 2-fold higher CD4+ T-cells/uL. Regarding nadir CD4 T-cell counts, Marin et al. reported an association of low nadir CD4 T-cell counts and any fatal NADM [68**], and Patel et al [22**] reported an association of low nadir CD4 T-cell counts with anal, colorectal, and lung cancers, but not with other cancers studied. Others have reported no association of nadir T-cell counts and any NADM [32**], anal cancer [26**,37**] and lung cancer [28**]. Finally, Bruyand et al. [33**] observed a higher risk of any NADM per year longer duration of CD4 <200 T-cells/uL (HR per year=1.16; 95% CI=1.03–1.30) and CD4 <500 T-cells/uL (HR per year=1.11; 95% CI=1.01–1.22).

Other measures of immune function

Others have provided additional evidence of an association of NADMs and immune status (Table 3). In the SMART trial [32**], patients enrolled in the CD4-guided episodic use of ART study arm had a similar risk of NADMs compared to control patients on continuous ART with an HR of 1.3 (95% CI: 0.7, 2.1), suggesting CD4 improvements with ART are not strongly associated with NADM risk. A small study in the Women's Interagency HIV Study evaluated the risk of any malignancy (ADM and NADM) and other markers of immune function, including Natural Killer (NK), NK T-cells and CD8 T-cells. Although baseline markers were not associated with malignancy, current NK T-cells were associated with a lower risk (HR per % higher=0.7; 95% CI=0.5–0.9) [72*].

A large meta-analysis by Grulich et al. [73**] compared cancers elevated in two populations known to have suppressed immune systems (i.e., persons with HIV or AIDS and organ transplant recipients). The authors included results from seven HIV or AIDS cancer match studies (n=444,712), and five cohorts of transplant recipients (n=31,977). Results indicated that NADMs elevated in both populations were largely related to infections including EBV-related cancers (Hodgkin's lymphoma), HBV/HCV-related cancers (liver), helicobacter pylori-related cancer (stomach), and HPV-related cancers (vulva/vaginal, penis, anal, oral

cavity/pharynx, non-melanoma skin, lip, esophagus, larynx, eye). Other malignancies elevated in both populations were lung and kidney cancers, multiple myeloma, and leukemia. A similarly designed but smaller study indicated that only liver cancer and the combined group of any NADM were elevated in persons with HIV or AIDS and transplant recipients [35*].

CONCLUSION

Several NADMs may have a lower risk with use of ART, including liver, breast, colorectal, and lung cancers. In addition, recent studies have indicated that certain individual NADMs appear to be associated with immunosuppression including Hodgkin's lymphoma, oral/pharynx, lung, anal, and colorectal cancers. Thus, continued ART use likely reduces the risk of certain NADMs with improved immune surveillance for malignancy. However, recent studies also indicated that rates of Hodgkin's lymphoma and anal cancer were increased in the ART era, and there has been no change in the risk of lung cancers. Thus, future studies should further characterize the epidemiology of NADMs in HIV-infected persons in the ART era, including changes in the prevalence of risk factors, co-infections, and screening practices in this population.

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Table 1

Recent literature evaluating calendar era changes in the risk of non-AIDS-defining malignancies

Author	Design	N	Subjects	Country	Cancer	Exposure	Results
Ferreros [21*]	Cohort	7,186	HIV(+) and HIV(−) IDU	Spain	Any NADM (fatal)	1987–96, 1997–2004	HIV(+): RR=1.3 (95% CI=0.7–2.4) HIV(−): RR=1.9 (95% CI=0.8–4.5)
Patel [22**]	Cohort	54,780	HIV(+)	USA	Multiple subtypes	1992–95, 1996–99, 2000–03	Increasing: anal (p<0.001), Hodgkin's (p=0.03), melanoma (p<0.05), colorectal (0.03), prostate (p=0.01). No significant trend for other cancers (p>0.05). Only anal cancer increased over time relative to general population (p<0.001).
Engels [23**]	Registry match	57,350	HIV(+)	USA	Multiple subtypes	1991–95, 1996–2002	Liver: RR=infinite (one-sided p=0.03) Hodgkin's: RR=2.7 (95% CI=1.0–7.1) Other cancers not significant (p>0.05)
Hessol [24*]	Registry match	14,210	AIDS	USA	Multiple subtypes	1990–95, 1996–2000	Anal: HR=2.7 (95% CI=1.0–7.3) All other cancers not significant (p>0.05)
Long [25*]	Cohort	2,566	HIV(+)	USA	Multiple subtypes	1996–97, 1998–99, 2000–01, 2002–03, 2004–05	No significant trend (p>0.05)
Piketty [26**]	Cohort	86,322	HIV(+)	France	Anal	1992–3/96, 4/1996–98, 1999–2000, 2001–02, 2003–04	Higher rates before vs. after 3/1996 (p>0.05). No trends between 4/1996–2004 (p>0.05)
Chaturvedi [27**]	Registry match	397,927	AIDS	USA	Lung	1980–89, 1990–95, 1996–2002	No significant trend (p>0.05)
Kirk [28**]	Cohort	2,086	HIV(+) and HIV(−) IDU	USA	Lung (fatal)	1988-6/96, 7/96-not stated	No significant trend (p>0.05)
Rimland [29*]	Cohort	2,999	HIV(+)	USA	Prostate	1982–2002, 2003-not stated	Increasing trend (p<0.001)
Crum-Cianflone [30]	Cohort	4,507	HIV(+)	USA	Skin	1987–96, 1997–2006	No significant trend (p>0.05)

HR, hazard ratio; IDU, injection drug users; NADM, non-AIDS-defining malignancy; RR, risk ratio

Table 2

Recent literature evaluating antiretroviral therapy use and risk of non-AIDS-defining malignancies

Author	Design	N	Subjects	Country	Cancer	Exposure	Results
Silverberg [32**]	RCT	5,472	HIV(+)	33 countries representing Asia; Africa; Australia; New Zealand; N. and S. America	Any NADM	ART duration	No significant association (p>0.05)
Bruyand [33**]	Cohort	4,194	HIV(+)	France	Any NADM	ART duration	No significant association (p>0.05)
Crum-Cianflone [34**]	Cohort	2,499	HIV(+)	USA	Any NADM	Nelfinavir or Indinavir use	No significant association (p>0.05)
Patel [22**]	Cohort	54,780	HIV(+)	USA	Multiple subtypes	Any ART use	Breast: RR=0.4; p=0.013 Colorectal: RR=0.5; p=0.027 Lung: RR=0.5; p<0.003 No significant association for other cancers (p>0.05)
Hessol [24*]	Registry match	14,210	AIDS	USA	Multiple subtypes	Current ART use	Liver: HR=0.3 (95% CI=0.1–0.9) All other cancers not significant (p>0.05)
Serraino [35*]	Cohort	10,949	HIV(+) and organ transplant recipients	France; Italy	Multiple subtypes	Any ART use	ART users and non users had similar risks for head and neck, liver, lung, Hodgkin's lymphoma, and any NADM
Steigbigel [36]	RCT	703	HIV(+)	Countries representing Asia; Australia; Europe; Peru; N. America; S. America	Multiple subtypes	Raltegravir use	No significant association (p>0.05)
D'Souza [37**]	Cohort	6,972	HIV(+) and HIV(−) MSM	USA	Anal	Current ART use	No significant association (p>0.05)
Piketty [26**]	Cohort	86,322	HIV(+)	France	Anal	Any ART use	HR=1.7 (95% CI=1.1–2.8)
Kirk [28**]	Cohort	2,086	HIV(+) and HIV(−) IDU	USA	Lung (fatal)	Any ART use	No significant association (p>0.05)
Crum-Cianflone [30]	Cohort	4,507	HIV(+)	USA	Skin	Any ART use	No significant association (p>0.05)

ART, antiretroviral therapy; HR, hazard ratio; MSM, men who have sex with men; IDU, injection drug users; NADM, non-AIDS-defining malignancy; RR, risk ratio

Table 3

Recent literature evaluating immune suppression and risk of non-AIDS-defining malignancies

Author	Design	N	Subjects	Country	Cancer	Exposure	Results
a. Immunosuppression based on AIDS diagnoses							
Marin [68**]	Cohort	10,661	HIV(+) with known dates of seroconversion	Australia; Canada; 15 European countries	Any NADM (fatal)	Prior AIDS	HR=2.5 (95% CI=1.2–5.0)
Engels [23**]	Registry match	57,350	HIV(+)	USA	Multiple subtypes	Prior AIDS	Oral/pharynx: RR=3.6 (95% CI=1.6–8.2) Lung: RR=2.3 (95% CI=1.4–3.5) Hodgkin's Lymphoma: RR=3.5 (95% CI=1.7–7.3) Other cancers not statistically significant
Piketty [26**]	Cohort	86,322	HIV(+)	France	Anal	Prior AIDS	HR=2.2 (95% CI=1.5–3.3)
Chaturvedi [27**]	Registry match	397,927	AIDS	USA	Lung	AIDS relative time	Higher rates post vs. pre-AIDS ($p<0.001$)
b. Immunosuppression based on CD4 T-cell counts							
Baker [69*]	RCT	1,397	HIV(+) initiating ART	USA	Any NADM	Current CD4	HR (per 100 cells/ul): 0.82 ($p<0.05$)
Bruyand [33**]	Cohort	4,194	HIV(+)	France	Any NADM	Duration low CD4	CD4<200: HR (per year)=1.16 (95% CI=1.03–1.30) CD4<500: HR (per year)=1.11 (95% CI=1.01–1.22)
Silverberg [32**]	RCT	5,472	HIV(+)	33 countries representing Asia; Africa; Australia; New Zealand; N. and S. America	Any NADM	CD4 nadir	No significant association ($p>0.05$)
Marin [68**]	Cohort	10,661	HIV(+) with known dates of seroconversion	Australia; Canada; 15 European countries	Any NADM (fatal)	CD4 nadir	<200 cells/ul: HR=2.7 (95% CI=1.1–6.6) 200–349 cells/ul: HR=3.2 (95% CI=1.4–7.2) ≥350 cells/ul (reference)
Monforte [70*]	Cohort	23,441	HIV(+)	Australia; USA; 21 European countries	Any NADM (fatal)	Current CD4	RR per doubling of CD4=0.61 (95% CI=0.57–0.66)
Bedimo [71**]	Cohort	100,260	HIV(+) / HIV(−) U.S. Veterans	USA	Multiple subtypes	CD4 at study entry	HIV(+) with any NADM, anal, and Hodgkins had lower CD4 vs. HIV(+) without cancer.
Engels [23**]	Registry match	57,350	HIV(+)	USA	Multiple subtypes	CD4 at HIV registration	No significant association ($p>0.05$) for any individual NADM
Patel [22**]	Cohort	54,780	HIV(+)	USA	Multiple subtypes	low CD4 nadir	Anal: RR=5.8; p=0.017 Colorectal: RR=6.3; p=0.013

Author	Design	N	Subjects	Country	Cancer	Exposure	Results
							Lung: RR=2.4; p=0.017
D'Souza [37**]	Cohort	6,972	HIV(+) and HIV(−) MSM	USA	Anal	CD4 nadir ≤200 cells/ul	HR=2.3 (95% CI=0.80–6.7)
Piketty [26**]	Cohort	86,322	HIV(+)	France	Anal	CD4 nadir	Lower risk with higher nadir CD4 (p>0.05)
Chaturvedi [27**]	Registry match	317,007	AIDS	USA	Lung	CD4 at AIDS registration	No significant association (p>0.05)
Kirk [28**]	Cohort	2,086	HIV(+) and HIV(−) IDU	USA	Lung (fatal)	CD4 nadir	No significant association (p>0.05)
b. Other measures of immune function							
Nowicki [72*]	Cohort	1,817	HIV(+) women	USA	Any malignancy	NK, NKT, and CD8 %	Baseline markers not significant (p>0.05) Current NKT: HR (per % higher) =0.7 (95% CI=0.5–0.9)
Grulich [73**]	Meta-analysis	476,149	HIV(+) or AIDS and organ transplant recipients	Australia; Canada; Denmark; England; Finland; Italy; Scotland; Sweden; Switzerland; USA	Multiple subtypes	Elevated SIR in both populations	NADMs elevated in both groups were Hodgkin's lymphoma, liver, stomach, vulva/ vaginal, penis, anal, oral cavity/pharynx, non-melanoma skin, lip, esophagus, larynx, eye, lung, kidney cancers, multiple myeloma, leukemia
Serraino [35*]	Cohort	10,949	HIV(+) and organ transplant recipients	France; Italy	Multiple subtypes	Elevated SIR in both populations	NADMs elevated (p>0.05) in both groups were any NADM and liver cancer
Silverberg [32**]	RCT	5,472	HIV(+)	33 countries representing Asia; Africa; Australia; New Zealand; N. and S. America	Multiple subtypes	CD4 guided ART use vs. continuous ART	No significant association (p>0.05)

ART, antiretroviral therapy; HR, hazard ratio; MSM, men who have sex with men; IDU, injection drug users; NADM, non-AIDS-defining malignancy; RR, risk ratio