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Factors contributing to risk for cancer among HIV-infected individuals, and evidence that earlier cART will alter this risk

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Abstract

Purpose of review—To critically appraise recent published literature about factors associated with cancer risk likely to be influenced by combination antiretroviral therapy (cART) in HIV-infected individuals, and the potential of earlier cART initiation to reduce this risk.

Recent findings—Factors leading to increased risk of non-AIDS defining malignancies (NADM) in particular remain poorly understood. Immunodeficiency appears to be key, whereas evidence is emerging that a direct pro-oncogenic effect of HIV, activated inflammatory and coagulation pathways, and cART toxicity may also contribute. By reducing HIV replication, improving immune function and limiting chronic inflammation, cART initiation at higher CD4+ cell counts may therefore reduce NADM risk. However, cART only partly normalizes enhanced inflammation and coagulation seen during HIV infection and conflicting laboratory and epidemiological data have been reported as to if (and how) cART affects NADM risk. Furthermore, secondary analyses of randomized controlled trials comparing early versus delayed cART initiation were inconclusive.

Summary—Continuous epidemiological surveillance is warranted to monitor trends in cancer incidence among HIV-infected individuals and to better understand the impact of earlier cART on NADM risk. The role of adjuvant anti-inflammatory or anti-thrombotic therapies to reduce cancer risk deserves further investigation.

Keywords

HIV; cancer; antiretroviral therapy; inflammation

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Introduction

Cancer and HIV infection have been inextricably intertwined since the beginning of the AIDS pandemic [1,2]. Three cancer types, namely Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and invasive cervical cancer (ICC), were soon found to have a particularly higher incidence in HIV-infected individuals and, for epidemiological surveillance purposes, have classically been referred to as AIDS-defining-malignancies (ADM) [3]. Including ICC in the list of ADM also served the purpose of emphasizing the importance of integrating gynaecologic care into medical services for HIV-infected women [3].

However, the spectrum of cancer types observed in excess in HIV-infected individuals was subsequently broadened to encompass a number of non-AIDS defining malignancies (NADM). With the advent of combination antiretroviral therapy (cART) resulting in prolonged life expectancy, the incidence of NADM rose more than 3-fold [4] and its burden has now surpassed the burden of ADM [4,5, ••6]. Moreover, when compared to the general population, HIV-infected individuals have been found to be at higher risk of NADM [7–9], with a standardised incidence ratio of approximately 2.0 [10]. Risk estimates differ considerably for individual NADM types. For instance, HIV-infected individuals have been shown to have, in large cohort studies, a 55-fold higher risk of anal cancer, 19-fold higher risk of Hodgkin lymphoma, 2.1-fold higher risk of non-melanoma skin cancer and 1.8-fold higher risk of melanoma and liver cancer [9,••11]. Of interest, the risk seems to be distinctly higher for those cancer types associated with viral infection and smoking [5,10,12,13], factors that are particularly prevalent in those with HIV. As a result, NADM are now a leading cause of death in the setting of HIV infection [•14].

The changing epidemiology of cancer during HIV infection has rendered the categorization of malignancies into ADM and NADM out-of-date. Anal cancer, a human papillomavirus (HPV)-related NADM, is more strongly associated with HIV infection than ICC [15], with incidence rates 80–110 times as high for HIV-infected men who have sex with men compared with the general population [••16,••17]. Moreover, the incidence of anal cancer was found to be 5-fold higher in HIV-positive than HIV-negative men who have sex with men [18]. Hodgkin lymphoma, an Epstein-Barr virus (EBV)-related NADM [19], is about 5 to 20 times more common in HIV-infected than in HIV-uninfected individuals [••11,20]. Hence, an emerging trend in recent studies is to categorize cancer into infection-related and infection-unrelated [5,7,9,10,12,21,••22].

The factors leading to an increased cancer risk among HIV-infected individuals remain poorly understood. Immunodeficiency and high prevalence of traditional cancer risk factors (e.g., smoking, oncogenic virus infection) [23–26] appear to be key, whereas evidence is emerging that a direct pro-oncogenic effects of HIV, activated inflammatory and coagulation pathways, and cART toxicity may also contribute [••6,••22,25,27]. It remains elusive, however, whether these factors act independently or synergistically. By reducing HIV replication, improving immune function and reducing inflammation at earlier stages of HIV infection, cART initiation at higher CD4+ cell counts has been proposed as a

potentially effective approach for reducing NADM risk [••6, 9,28,29]. The purpose of this review is to critically appraise recent evidence regarding established and suspected factors associated with cancer risk likely to be influenced by cART, including immunodeficiency, HIV viral load, enhanced inflammation and coagulation, cART toxicity, and the potential of earlier cART initiation to reduce this risk. We focused on Medline-indexed English literature published from June 2012 to June 2013 that evaluated cART effects, including immunodeficiency and viral replication, on NADM risk. In this review, we will not address traditional cancer risk factors.

Immunodeficiency

The strong relationship between lower CD4+ count (i.e., immunodeficiency) and increased ADM risk is well-established [••6]. Furthermore, there is mounting evidence for an inverse relationship between CD4+ count and NADM risk as well [••6]. Although earlier studies that used static (i.e., time-fixed) CD4+ measures were inconsistent regarding this relationship, more recent studies that used time-updated measures of CD4+ count have observed associations between lower recent CD4+ count and increased risk of NADM (grouped) and of a range of specific cancer types. These reports have been reviewed in detail elsewhere [••6]. As mentioned above, HIV-infected individuals have been found to be at a particularly higher risk of infection-related NADM [5,10,12,13]. Moreover, infection-related NADM may be diagnosed at later stages and may be associated with elevated morbidity and mortality in people with HIV infection [30–32]. On the other hand, the augmented risk of infection-unrelated NADM observed among individuals with lower CD4+ cell counts [9,28,29,33–36] is consistent with a possibly impaired surveillance of pre-malignant and malignant cells (or with an unknown viral component to cancer types that are currently considered infection-unrelated). Thus, HIV-associated immunodeficiency appears to exert its cancer-predisposing effects through two main mechanisms: (1) reduced clearance and control of oncogenic virus infection and (2) reduced immune surveillance of malignant cells.

HIV viral load and direct oncogenic effects of HIV

Some studies have reported an association between ongoing viral replication and cancer risk. In one report, both cumulative and current HIV RNA levels >500 copies/mL were independently associated with increased risk of ADM [37]. In another study, a direct relationship was found between current HIV RNA level and risk of KS and NHL, and between duration of time with HIV RNA >100,000 copies/mL and anal cancer risk [28]. Evidence has accrued indicating that HIV itself, via tat and Vpr proteins, may have direct pro-oncogenic effects. The potential mechanisms are multiple and complex, involving synergism with other pro-oncogenic viruses [38], disruption of cell cycle regulation [39], blockage of tumour suppressor gene function [40], promotion of chromosome instability through the inhibition of telomerase activity [41], impairment of DNA repair function [42], induction of tumour angiogenesis [38,43] and enhancement of the effects of exogenous carcinogens [44,45].

Enhanced inflammation and coagulation

More recently, evidence has emerged linking activated inflammatory and coagulation pathways, as demonstrated by higher plasma levels of biomarkers, to cancer risk. In The

Strategies for Management of Antiretroviral Therapy (SMART) Study [46], structured cART interruptions were reciprocally associated with higher levels of coagulation and inflammatory biomarkers [47] and increased risk of cancer [48]. In a recent study of ours, we investigated the relationship between plasma levels of interleukin-6 (IL-6), a pro-inflammatory cytokine, C-reactive protein (CRP), an inflammatory marker whose hepatic production is stimulated by IL-6, and D-dimer, a fibrin-degradation product and marker of enhanced coagulation, and the risk of cancer among 5,000 HIV-infected individuals enrolled in the control arms (i.e., standard of care) of three randomized trials [••22]. Increasing baseline biomarker plasma levels were independently associated with higher cancer risk; the hazard ratio (HR) per doubling in biomarker level was 1.38 ($P < 0.001$) for IL-6, 1.16 ($P = 0.001$) for CRP, and 1.17 ($P = 0.03$) for D-dimer. Results were similar for infection-related and infection-unrelated cancers. This association was strongest for IL-6, the only biomarker that remained significantly associated with cancer risk with simultaneous adjustment for all three markers. Although not providing definitive evidence for a causal link between enhanced inflammation/coagulation and cancer risk during HIV infection, these findings do indicate that trials of interventions that reduce inflammatory and coagulation biomarker levels, in particular IL-6, may be warranted.

cART toxicity

With regard to cART toxicity as a risk factor for cancer, a number of studies have failed to detect positive associations between cART use and cancer risk [49–52]. Furthermore, the beneficial effects of cART on HIV replication, immune function, and inflammation suggest that cART use would lead to a reduction in overall cancer risk [••6,9,28,29]. Nevertheless, potential carcinogenic effects of specific cART agents and drug classes may result in increased risk of cancer. This is the case not only for toxic, older drugs, such as zidovudine [53,54], but also for antiretrovirals currently recommended as first-line therapy for treatment-naïve patients. Protease inhibitors have been linked to a higher risk of anal cancer in observational studies after adjustment for important confounders [••55–57] and efavirenz, a non-nucleoside reverse transcriptase inhibitor, was associated with increased risk of Hodgkin lymphoma in one study [58]. In a recent report, raltegravir, an integrase inhibitor, was found to induce host DNA rearrangements, which, from a theoretical point of view, may have unforeseen consequences including an increased risk of cancer [59]. It is also biologically plausible that, by reducing immunological surveillance of malignant cells, CCR5 inhibitors, a drug class increasingly used in treatment-experienced individuals who failed previous cART regimens, may also lead to an increased incidence of NADM [60]. However, in the absence of any epidemiologic evidence, the clinical relevance of the potential carcinogenic effects of integrase and CCR5 inhibitors remains to be determined.

Would earlier ART initiation reduce the risk of NADM?

There is global consensus that the overall risk:benefit ratio of cART initiation at CD4+ cell counts below 350 cells/mm^3 is favourable. However, given the lack of randomized trial evidence and inconsistent results from observational studies [61,62], a debate on whether and when to initiate cART at higher CD4+ cell count thresholds is still unfolding [•63, •64]. This has resulted in inconsistencies among treatment guidelines. The US Department of Health and Human Services guidelines [65] recommend cART for all HIV-infected persons,

regardless of CD4+ cell count (i.e., no threshold), whereas the British HIV Association guidelines only recommend cART initiation in asymptomatic persons with CD4+ counts below 350 cells/mm^3, an exception being serodiscordant couples, where cART can be initiated in asymptomatic HIV-positive individuals with higher CD4+ counts to reduce the risk of transmission to the HIV-negative partner [66]. The World Health Organization (WHO), in its newest guidelines, recommends cART initiation when CD4+ cell counts drop below 500 cells/mm^3 [67]. Earlier cART initiation has clear benefits in terms of reduced HIV transmission at the population level [68], but is not without potential drawbacks in individuals with early HIV infection and thus low risk of disease progression, including cART toxicity, risk of drug resistance and required commitment to life-long therapy.

There is evidence that earlier cART initiation, by preventing immune deterioration associated with the decline in CD4+ cell counts, reduces KS and NHL risk [69–71]; indeed, cART initiation results in regression of early stage KS [72]. Furthermore, because cART improves immune function, lowers HIV viral load, and reduces inflammation, earlier cART initiation has been suggested as a potential approach for reducing NADM risk as well, among HIV-infected individuals [••6,9,28,29]. Thus, reduced incidence [•73, •74] and even regression of HPV-related pre-malignant squamous intraepithelial lesions [•75] following cART initiation have been reported. Alongside their potential benefit in terms of cancer prevention through immune reconstitution and reduced inflammation and viral suppression, some drugs used in cART regimens have been found to have a direct anti-neoplasic effect. In *in vitro* and *in vivo* experiments, protease inhibitors were shown to block angiogenesis [76,77] and inhibit tumour growth and invasion [77]. Similarly, efavirenz was found to have selective anti-tumour cytoxic effects [78] and to inhibit proliferation and differentiation of neoplasic cells [79]. However, the clinical relevance of these findings is yet to be determined and, as discussed above, conflicting laboratory and epidemiological evidence suggests that some cART agents or classes may be associated with increased NADM risk.

The definitive way to determine the effect of earlier cART initiation on risk of NADM is to conduct a large, cancer endpoint-driven randomized controlled trial. However, such a trial would require a very large sample size with extended follow-up. Currently, additional randomized evidence to inform this debate can be obtained only from secondary analyses of trials in which cancer events were not primary endpoints. For two [80,81] of three contemporary randomized trials comparing immediate versus delayed cART initiation in treatment-naïve patients [68,80,82], data on NADM outcomes have been reported (Table 1), with no difference noted between the two strategies. The number of NADM events was, however, too small and much longer follow-up will be required to demonstrate differences (if any) between early versus deferred cART initiation. The deferred strategy in these trials allowed CD4+ cell counts to drop far below the thresholds currently recommended for cART initiation by the majority of treatment guidelines [65,66,83]. In this respect, data from the ongoing Strategic Timing of AntiRetroviral Treatment (START) study [84], a large (N=4,600) randomized trial, will be of particular interest. This study, with a composite clinical endpoint including NADM, is comparing immediate versus deferred (i.e., when CD4+ counts drop below 350) cART initiation in HIV-positive persons with CD4+ counts higher than 500 cells/mm^3.

Finally, virological suppression induced by cART only partly normalizes the activated inflammatory and coagulation pathways observed in persons with HIV [85,86]: the reduction of T-cell activation as a result of effective therapy does not reach the level of HIV-uninfected controls [87]. Should activated inflammatory or coagulation pathways be demonstrated definitively to play a causal role in carcinogenesis among HIV-infected individuals, adjunctive anti-inflammatory or anti-thrombotic therapies may be required to further reduce cancer risk in this population [••22]. In an AIDS Clinical Trial Group observational study investigating whether statin use is associated with decreased risk of serious non-AIDS-defining events [••88], statin use was found to be associated with a 57% reduction in NADM risk. As no significant benefits were observed for cardiovascular events, it was hypothesized that the reduction in cancer risk was driven by cholesterol-independent, anti-inflammatory properties of statins. On the other hand, the lack of an inverse association between statin use and cardiovascular events may also be explained by unknown biases (as such an association would be expected) or by low statistical power for cardiovascular events (adjusted and weighted HR = 0.89; 95% confidence interval = 0.32–2.44). However, the report findings are consistent with a case-control study nested within an HIV cohort in which statin exposure, but not use of other lipid lowering drugs, was found to be associated with a significantly decreased risk of NHL [89], a cancer type whose development was shown be preceded by chronic immune activation [90,91].

Conclusion

Cancer, in particular NADM, imposes a growing burden on the aging population of HIV-infected individuals. Immunodeficiency and high prevalence of traditional cancer risk factors (e.g., smoking, oncogenic virus infection) appear to be key to the increased cancer risk observed in this population, whereas evidence is emerging that a direct pro-oncogenic effect of HIV, activated inflammatory pathways, and cART toxicity may also contribute to the higher risk. Because cART improves immune function, lowers HIV viral load, and reduces inflammation, cART initiation at higher CD4+ cell counts has been proposed as a potentially effective approach to reducing NADM risk. cART is, however, not without risks and there is no conclusive laboratory or epidemiological evidence regarding the association of cART and NADM risk. Therefore, continuous epidemiological surveillance is warranted to monitor trends in cancer incidence among HIV-infected individuals and to better understand the impact of earlier cART on NADM risk. Since cART alone only partly normalizes the enhanced inflammation and coagulation associated with HIV infection, the role of adjuvant anti-inflammatory or anti-thrombotic therapies to reduce NADM risk deserves further investigation.

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Abbreviations

ADM	AIDS defining malignancies
cART	combination antiretroviral therapy
CCR	C-C chemokine receptor type 5
CRP	C-reactive protein
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HR	Hazard ratio
ICC	invasive cervical cancer
IL-	interleukin-6
KS	Kaposi sarcoma
NADM	non-AIDS defining malignancies
NHL	non-Hodgkin lymphoma
RNA	Ribonucleic acid
SMART	The Strategies for Management of Antiretroviral Therapy Study
START	Strategic Timing of AntiRetroviral Treatment Study
WHO	World Health Organization

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• of special interest

•• of outstanding interest

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Key Points

- Cancer, in particular non-AIDS defining malignancies (NADM), imposes a growing burden on HIV-infected individuals. Immunodeficiency appears to be key to the increased cancer risk observed in this population, whereas evidence is emerging that a direct pro-oncogenic effect of HIV, activated inflammatory and coagulation pathways, and combination antiretroviral therapy (cART) toxicity may also contribute.
- Because cART improves immune function, lowers HIV viral load, and reduces inflammation, cART initiation at higher CD4+ cell counts has been proposed as a potentially effective approach to reducing NADM risk.
- Nevertheless, cART only partly normalizes the enhanced inflammation associated with HIV infection and conflicting laboratory and epidemiological data have been reported as to if (and how) cART affects cancer risk.
- Continuous epidemiological surveillance is warranted to better understand the impact of earlier cART on NADM risk. The role of adjuvant anti-inflammatory or anti-thrombotic therapies to reduce cancer risk deserves further investigation.

Table 1

Impact of immediate vs. deferred initiation of cART on NADM incidence: data from randomized controlled trials involving cART-naïve HIV+ persons

Study	Sample size	Median follow up time (years)	Median baseline CD4+ count (cells/mm^3)	Deferral Strategy	Median CD4+ count (cells/mm^3) at cART initiation in the deferred arm	NADM in immediate cART initiation arm	NADM in deferred cART initiation arm	Relative risk (95% CI) for NADM (immediate vs. deferred cART)
SMART[a] [80]	249	2.6	437	cART deferred until: **1** CD4+ declined to < 250 cells/mm^3 **2** CD4+ percentage declined to < 15% **3** Symptoms of HIV disease developed	245	0/131	0/118	n/a
HPTN 052 [81]	1761	2.1	428	cART deferred until: **1** CD4+ declined to ≤ 250 cells/mm^3 **2** AIDS-defining illness developed	229	3/886	3/875	0.99 (0.20–4.88)
Pooled data from the two trials						3/1017	3/993	0.98 (0.20–4.83)

[a]Only includes the sub-set of patients who were treatment-naïve at study entry