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"Combination antiretroviral therapy and cancer risk"

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Abstract

Purpose—to review the newest research about the effects of combination antiretroviral therapy (cART) on cancer risk

Recent findings—HIV+ persons are at increased risk of cancer. As this risk is higher for malignancies driven by viral and bacterial co-infections, classifying malignancies into infection-related and infection-unrelated has been an emerging trend. Cohorts have detected major reductions in the incidence of Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL) following cART initiation among immunosuppressed HIV+ persons. However, recent randomized data indicate that cART reduces risk of KS and NHL also during early HIV infection before overt immunosuppression occurs. Long term effects of cART exposure on cancer risk are not well defined; according to basic and epidemiological research, there might be specific associations of each cART class with distinct patterns of cancer risk.

Summary—The relationship between cART exposure and cancer risk is complex and nuanced. It is an intriguing fact that, whether initiated during severe immunosuppression or not, cART reduces risk of KS and NHL. Further research should identify mediators of the benefit of immediate cART initiation in reducing cancer risk, understand the relationship between long term cART exposure and cancer incidence, and assess whether adjuvant anti-inflammatory therapies can reduce cancer risk during treated HIV infection.

Keywords

HIV; cancer; antiretroviral therapy; lymphoma; Kaposi sarcoma

Introduction

HIV+ persons are at increased risk of cancer when compared to the general population. This risk seems to be higher for malignancies driven by viral and bacterial co-infections [1-••9], although HIV+ persons also have excess risk of infection-unrelated malignancies [10]. The question as to how combination antiretroviral therapy (cART) influences cancer risk has been debated since the beginning of the AIDS epidemics. During HIV infection, cancer risk seems to be determined by a complex interaction between prolonged life expectancy [1], traditional risk factors [11-12], pro-oncogenic viruses co-infection, potentially direct

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oncogenic effects of HIV [13-15], cART toxicity [16, ••17, •18] and activated inflammation and coagulation [19-23]. It is thus difficult to disentangle the direct effect of cART on cancer risk from other factors postulated to pay a role in carcinogenesis.

Since cART became available in the late nineties, Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL) have been the two malignancies that experienced the greatest decline in incidence [24-27]. At that time, cART was usually initiated late in the course of HIV infection when CD4 cell counts dropped below a given threshold [28,29]. Because cART improves immune function by suppressing viral replication, the reduced incidence of KS and NHL was considered as evidence to link immunosuppression to cancer development during HIV infection. This view was reinforced by reports demonstrating similar distribution of malignancies at excess risk among other immune impaired populations [30-32]. Furthermore, immunosuppression, as measured by declines in CD4 counts, is linked to a higher risk of not only classical AIDS-defining cancers but also of infection-unrelated cancers [33-45].

In the light of new evidence, however, this view may be too simplistic. Recent randomized data indicate that cART reduces risk of KS and NHL also during early HIV infection before the development of overt immunosuppression [••46]. This benefit is measurable in the short term and reported in one trial with relatively short follow up [••46]. The long term effect of cART exposure on cancer risk, however, is not well defined and some cohort studies have demonstrated an independent link between long term cART exposure and cancer risk [16, ••17, •18, 47]. Taken together, these findings point out a more complex and nuanced relationship between cART exposure and cancer risk than previously thought.

Here, we set out to review the newest research about the effects of cART on cancer risk in the setting of HIV infection. PubMed was searched with the terms “HIV”, “cancer”, “AIDS”, “combination antiretroviral therapy” and “antiretrovirals” together with generic and brand names for the most commonly used antiretrovirals. Recent reports from the last two years were prioritised although seminal papers are referred to irrespective of publication date. Relevant reviews and abstracts presented at conferences but not yet published are also discussed. Whenever available, randomised data had precedence over cohort studies to support our statements.

How to best categorise malignancies?

Studying associations between cART exposure and cancer risk is complicated by the relatively rare occurrence of cancer events. Although studies should ideally look into individual cancer types, grouping malignancies in broader categories may be inevitable to have power enough to detect small differences in risk. This is particularly the case for clinical trials where follow up usually do not exceed a couple of years.

The classical categorisation of malignancies into AIDS-defining and non-AIDS-defining malignancies was first introduced in the early nineties for surveillance purposes [48]. The diagnosis of an AIDS-defining malignancy was an indicator of progression to AIDS, thus prompting HIV testing and treatment initiation. Drawbacks of this classification were

subsequently made evident by the fact that malignancies not included in the classification of AIDS-defining also disproportionally affect HIV+ persons [2,5-7,42].

Epidemiological surveillance has demonstrated that HIV infection and other immunosuppression states increase the risk of malignancies associated with viral and bacterial co-infections [1-••9]. As a result, the classification of cancer into infection-related and infection-unrelated malignancies has been an emerging trend in HIV research [49, ••50]. As pointed out by others [51], this classification is not perfect because, even when considering a given cancer type such as NHL, an infectious origin can only be ascertained in a subset of cases. This classification can only be definitive after a thorough search for pathogens in tissue samples using *in situ* hybridization [52,53]. Despite these difficulties, classifying malignancies into infection-related and infection-unrelated seems to us more appropriate than into AIDS-defining and non-AIDS-defining. It takes into account the evolving new data from epidemiological surveillance and establishes a framework to study the interplay between HIV, bacterial and viral co-infections and cancer. However, published reports continue to use either classification indiscriminately. Not surprisingly, this makes comparisons across studies difficult.

Does cART reduce cancer risk?

Cohort data—Soon after the advent of cART, observational studies have detected a major reduction in the incidence of KS and NHL following cART initiation among treatment naïve HIV+ persons [24-27]. cART initiation, however, was not universally recommended. cART was to be postponed until significant declines in CD4 cell counts occurred but there was no agreement among guidelines as to the CD4 threshold bellow which cART should be initiated [28,29]. The benefit of cART in reducing cancer risk would be explained by suppression of HIV replication, immune function improvement or reduction of inflammation. The majority of studies [33-45], but not all [26,54,55], also pointed out a decreased incidence of malignancies not driven by infection with increased cART exposure. Therefore, global improvement of immune surveillance against cancer cells was also postulated as a likely mediator of cART benefit in reducing cancer risk [49].

However, experimental data suggest that specific antiretrovirals and drug classes may have potential carcinogenic effects [56,57]. This could give opportunity for cancer to develop during the prolonged lifespan brought about by cART initiation. There is now a wide range of cART regimens which physicians and HIV+ persons initiating treatment can choose from [58-61]. According to basic and epidemiological research, there might be specific associations of each cART class with distinct patterns of cancer risk.

Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens were associated with increased risk of non-AIDS-defining cancers and Hodgkin lymphoma in one study [62]. This finding, however, was not replicated in other cohorts [16;••17]. Indeed, cell culture studies identified a potential anti-neoplastic effect of efavirenz [63]. This is an example of how basic and epidemiological research has reached discrepant conclusions about the effects of cART exposure on cancer risk. Inherent study design limitations, different methodological approaches, variable follow up time and distinct categorizations of malignancies are likely explanations for discrepant findings.

In animal studies, protease inhibitors (PIs) were found to have a potent anti-angiogenic effect and to induce regression of KS [64,65]. It was expected, in clinical practice, that PI-based cART would reduce the incidence of KS more than other cART regimens. However, NNRTI-based and PI-based regimens were equally effective in reducing incidence of KS in cohort studies [66,67]. A recent trial involving cART naïve patients with KS compared PI-based to NNRTI-based cART for a composite endpoint of death or requirement for systemic chemotherapy [•68]. PI-based regimens were not superior to NNRTI-based cART. Therefore, despite strong biological plausibility [64,65], regression of KS after cART initiation cannot be attributable to the effects of specific antiretrovirals.

In epidemiological studies, PI-based regimens were independently associated with increased risk of anal cancer. This finding was replicated in at least three different cohorts [16, ••17, •18]. It is important to monitor this association because the incidence of anal cancer is increasing significantly among HIV+ persons [6,69]. As for a composite endpoint of non-AIDS-defining cancers, an increased risk was observed with cumulative exposure to PI-based cART in one study [••17] but not in other [16]. No clear pathophysiological mechanism has been proposed to explain this possible association. From our studies, PI-based regimens were linked to higher levels of IL-6 [70], a cytokine involved in all stages of cancer development [71]. Elevated plasma levels of IL-6 and other biomarkers of activated inflammation and coagulation were linked to future risk of both infection-related and infection-unrelated malignancies among HIV+ persons [19-21;23]. In one randomised trial, participants switching away from PI-based regimens experienced significant reductions in IL-6 levels when compared to participants continuously receiving PIs [72].

Integrase inhibitors and C-C chemokine receptor type 5 (CCR5) inhibitors have only recently been used in clinical practice. As a result, most HIV cohorts have not had enough follow up time to study associations between the new drugs and rare clinical outcomes such as cancer. DNA rearrangements caused by integrase inhibitors could potentially lead to an increased risk of cancer [73]. A recent cohort study compared cancer incidence between participants receiving or not raltegravir-based regimens [•74]. No difference in cancer risk was observed. CCR5 inhibition can potentially reduce immune surveillance of malignant cells; in one trial involving treatment experienced participants, 4 of 90 vicriviroc recipients and none of 28 control subjects developed lymphoma [75]. This signal, however, has not been confirmed by other studies and vicriviroc treatment seems to have no effect on Epstein-Bar virus reactivation [76]. At the moment, there is no epidemiologic evidence for causal relationship between use of integrase inhibitors or CCR5 inhibitors and cancer risk. However, continued epidemiological surveillance and longer cohort follow up are required to confidently exclude a small cancer risk.

Randomised data—Following the ground breaking results of recent trials [••77,••78,••79], cART is now universally recommended irrespective of CD4 cell count thresholds [58-61]. At the individual level, the benefit of immediate cART initiation is evident for a composite endpoint of serious AIDS-defining and non-AIDS-defining events. A closer look into cancer events has also pointed out measurable benefits of immediate cART in reducing cancer risk [••46].

The Strategic Timing of Antiretroviral Therapy (START) study randomized HIV+ adults with a CD4 count over 500 cells/mm^3 to immediate cART initiation or cART deferral until CD4 counts dropped below 350 cells/mm^3 [••77]. Immediate cART initiation reduced the overall risk of cancer by 64% [••77]; corresponding risk reduction figures were 74% for infection-related cancer (Hazard ratios [HR]; 95% confidence interval [CI]: 0.26; 0.11-0.64; p=0.003) and 51% for infection-unrelated cancer (HR; 95% CI: 0.49; 0.21-1.15; p=0.103) [••46]. The benefit of immediate cART initiation in reducing cancer risk was mainly driven by a reduction in cases of KS and NHL. These findings demonstrate that an immunossupressed host is not a necessary requirement for KS and NHL to develop. Furthermore, as START participants did not have overt immunossupression, the benefit of immediate cART in reducing cancer cannot be entirely attributable to improvement of immune function. Alternatively, it is possible that CD4 cell count, as a marker of immune function, may not capture a subtler immune impairment present during untreated HIV infection and potentially linked to cancer development.

Recent reports indicate that a growing proportion of KS and NHL cases are diagnosed among HIV+ persons with CD4 cell counts above 500 cells/mm^3 and undetectable viral load [80-•83]. The clinical meaning of this is unclear. It was hypothesized that KS and NHL cases arising among cART-treated persons with high CD4 cell counts may be biologically distinct and carry a worse prognosis [81; •83]. However, one study found that cART-treated persons with CD4 cell counts above 300 cells/mm^3 who developed KS had a longer survival than those diagnosed with KS at lower CD4 counts [84].

The impact of cART initiation on the risk of infection-unrelated or non-AIDS-defining cancer is more difficult to quantify because there are few randomised trials reporting these cancer events among HIV+ persons initiating treatment (Figure 1). Pooled data from these trials [••77,••78,85-87] indicate that immediate cART initiation may reduce the risk of non-AIDS-defining cancer by 29% when compared to cART deferral (Risk ratio [RR]; 95% CI: 0.71; 0.36-1.40; p=0.32) (Figure 1). This risk reduction is not significant most probably because the short follow up of trials did not give enough opportunity for less common malignancies to develop. Indeed, we found no statistical significance when we tested the difference in HRs for infection-related versus infection-unrelated cancer in START (p= 0.27) [••46].

Another informative trial for the debate on how cART use influences cancer risk was the Strategies for Management of Antiretroviral Therapy (SMART) study [88]. SMART compared, in individuals with CD4 cell count above 350 cells/mm^3 at baseline, continuous cART use (viral suppression [VS] arm) versus structured cART interruptions guided by CD4 cell counts (drug conservation [DC] arm). Structured treatment interruptions were associated with a significantly higher risk of AIDS-defining malignancies (HR DC/VS; 95% CI: 5.5; 1.2-25.0; p=0.03). No significant effect on the risk of non-AIDS-defining cancer was observed (HR DC/VS; 95% CI: 1.3; 0.7-2.1; p=0.40) [89]. However, given the low numbers of cancer events, a modest effect of cART interruption on the risk of non-AIDS-defining cancer could not be entirely excluded as demonstrated by the upper limit of CI. An individual participant data analysis combining SMART and START will be helpful to

quantify accurately the impact of immediate and continuous cART, the strategy recommended by current treatment guidelines, on cancer risk.

How does cART reduce cancer risk?

In the setting of overt immunosuppression, the benefit of cART initiation in reducing cancer risk seems to be largely mediated by suppression of HIV replication and immune function recovery. This is corroborated by the fact that persons with persistent declines in CD4 counts or with suboptimal immune recovery following cART initiation continue at increased risk of cancer [33-44]. However, cART also reduces cancer risk when initiated among HIV+ persons with early HIV infection and CD4 cell counts above 500 cells/mm^3[••46]. It is an intriguing fact that, whether initiated during severe immunosuppression or not, cART has a measurable effect on the risk of the same infection-related malignancies, namely KS and NHL. This calls for a better understanding of the mechanisms by which cART lowers cancer risk among persons with high CD4 counts.

Contrary to what we hypothesized, adjustment for CD4 counts had no impact on the protective effect of immediate cART on cancer risk among START participants and adjustment for HIV RNA levels only partially attenuated this association [••46]. Though limited by a small sample size and relatively short follow-up, our findings suggest that benefit of immediate cART doesn't appear to be solely attributable to HIV RNA suppression and may also be mediated by other mechanisms, such as a curb on oncogenic virus coinfection and reduction of inflammation.

Recent data suggests that HIV may be directly involved in lymphomagenesis [90,91]. HIV-derived p17 secreted within lymphoid tissues promotes microenvironment changes that may foster lymphoma development [90]. Sequencing studies have demonstrated that HIV isolated from lymphoma tissue is genetically distinct from HIV present in normal tissues [92]. Upon cancer diagnosis and metastasis, the genetic diversity of HIV may be increased within cancer tissues [93]. Furthermore, in some studies, HIV RNA levels were associated with subsequent development of lymphomas [94,95]. It is possible that cART reduces lymphoma risk by directly interfering with HIV-associated lymphomagenesis. As Epstein-Bar virus [EBV] latency patterns observed in NHL tissue differs between pre- [96] and post-cART studies [97], it was also hypothesised that cART may improve immune surveillance of proteins expressed by cells latently infected by EBV resulting in a shift to a less oncogenic latency pattern [97].

It is unclear how cART interferes with mechanisms promoting carcinogenesis in HIV+ persons with high CD4 cell counts. Elevated levels of biomarkers are associated with increased risk of infection-related and infection-unrelated cancer [19-23]. Thus, reduction of inflammation could be an important mechanism explaining the lower risk of cancer observed after cART initiation. However, cART does not entirely normalise the enhanced inflammation and hypercoagulation state characteristic of HIV disease [98-100]. This raises the question as to whether adjuvant anti-inflammatory therapies could further reduce cancer risk among cART-treated HIV+ persons. Observational studies have reported a lower cancer risk among HIV+ persons receiving statins [101-104]. The Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults

(REPRIEVE) trial will randomise 6,500 HIV+ individuals to start statins or placebo [105]. REPRIEVE has cardiovascular disease as the primary endpoint but may also provide an opportunity to investigate the effect of statins on cancer incidence during treated HIV infection.

Conclusion

The relationship between cART exposure and cancer risk is complex and nuanced. Recent randomized data indicate that immediate cART initiation reduces risk of KS and NHL during early HIV infection before the development of overt immunosuppression. The long term effect of cART exposure on cancer risk, however, is not well defined and some cohort studies have demonstrated an independent link between PI exposure and risk of anal cancer. Further research should identify mediators of the benefit of immediate cART initiation in reducing cancer risk, understand the relationship between long term cART exposure and cancer incidence, and assess whether adjuvant anti-inflammatory therapies can reduce cancer risk during treated HIV infection.

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Conflicts of Interest

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Abbreviations

cART	combination antiretroviral therapy
CCR5	C-C chemokine receptor type 5
CI	confidence interval
DC	drug conservation
EBV	Epstein-Barr virus
HIV	human immunodeficiency virus
HR	Hazard ratio
IL-6	interleukin-6
KS	Kaposi sarcoma
NHL	non-Hodgkin lymphoma
NNRTI	Non-nucleoside reverse transcriptase inhibitors
PI	protease inhibitors

REPRIEVE	Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults
RNA	Ribonucleic acid
SMART	The Strategies for Management of Antiretroviral Therapy Study
START	Strategic Timing of AntiRetroviral Treatment Study
VS	viral suppression

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• of special interest

•• of outstanding interest

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Key Points

- HIV+ persons are at increased risk of cancer when compared to the general population. Epidemiological surveillance has demonstrated that HIV infection and other immunosuppression states increase the risk of malignancies associated with viral and bacterial co-infections.
- Studying associations between cART exposure and cancer risk is complicated by the relatively rare occurrence of cancer events. Classifying malignancies into infection-related and infection-unrelated is more appropriate than into AIDS-defining and non-AIDS-defining. This classification takes into account the evolving new data from epidemiological surveillance and establishes a framework to study the interplay between HIV, bacterial and viral co-infections and cancer.
- In the setting of overt immunosuppression, the benefit of cART initiation in reducing cancer risk seems to be largely mediated by suppression of HIV replication and immune function recovery. However, cART also reduces cancer risk when initiated among HIV+ persons with early HIV infection and CD4 cell counts above 500 cells/mm^3.
- It is an intriguing fact that, whether initiated during severe immunosuppression or not, cART has a measurable effect on the risk of the same infection-related malignancies, namely Kaposi sarcoma and non-Hodgkin lymphoma.
- The long term effect of cART exposure on cancer risk is not well defined. Some cohort studies have demonstrated an independent link between long term cART exposure and cancer risk. Reported associations between PI exposure and anal cancer warrant further investigation.
- Further research is needed to identify mediators of the benefit of immediate cART initiation in reducing cancer risk, to better understand the relationship between long term exposure to cART and cancer incidence, and to assess whether adjuvant anti-inflammatory therapies can further reduce cancer risk during treated HIV infection.

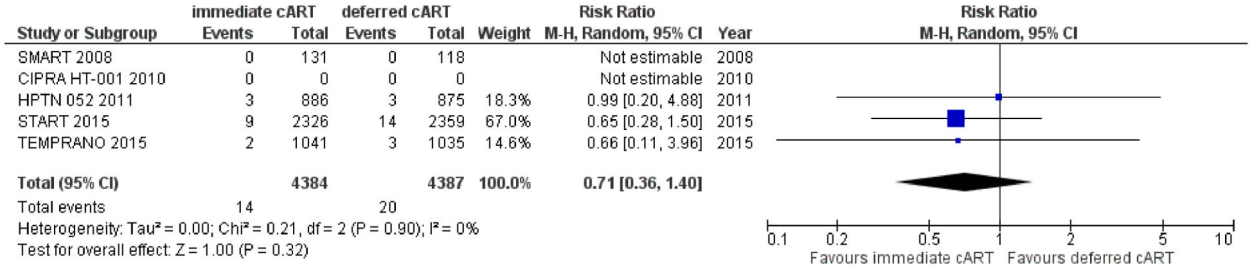

Figure 1. Effect of immediate vs deferred cART initiation on non-AIDS-defining cancer: randomized controlled trials among treatment-naïve HIV+ persons

In SMART, only data from the subset of treatment naïve participants at study entry is included [85]. Cancer outcomes were not reported in CIPRA HT [86]. Arms with and without isoniazid preventive therapy (IPT) were combined in TEMPRANO [••78].

Abbreviations: CIPRA HT 001: Comprehensive International Program of Research on AIDS; HPTN: HIV Prevention Trials Network; SMART: The Strategies for Management of Antiretroviral Therapy Study; START: Strategic Timing of AntiRetroviral Treatment Study; TEMPRANO: Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults.