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HIV-1, HAART and cancer: a complex relationship

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List of abbreviations

AIDS, acquired immune deficiency syndrome
CCR5, C-C chemokine receptor type 5
EBV, Epstein–Barr virus
HAART, highly active antiretroviral therapy
HHV, human herpes virus
HIV, human immunodeficiency virus
HPV, human papillomavirus
HBV, hepatitis B virus
HCV, hepatitis C virus,
INSTI, HIV-integrase strand transfer inhibitor
KS, Kaposi sarcoma
LINE-1, long interspersed nuclear element-1
MMP, matrix metalloproteinases
NHL, non-Hodgkin lymphoma
NNRTI, non-nucleoside reverse transcriptase inhibitor
NRTI, nucleoside reverse transcriptase inhibitor

PI, HIV-protease inhibitor
PI3K, phosphatidylinositol 3-kinase
PSA, prostate-specific antigen
VEGF, vascular endothelial growth factor

Declarations

Authors' contributions

All authors equally contributed to the manuscript. All authors read and approved the final manuscript

Declaration of interests

The authors declare that they have no conflict of interests

Availability of data and material

All data generated or analyzed during this study are included in this published article

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Abstract

HIV infected people are at higher risk of developing cancer, although it is globally diminished in the era of highly active antiretroviral treatment (HAART). Recently, antioncogenic properties of some HAART drugs were discovered. We discuss the role of HAART in the prevention and improvement of treatment outcomes of cancers in HIV-infected people. We describe different trends in HAART-cancer relationships: cancer-predisposing as well as cancer-preventing. We cover the roles of particular drug regimens in cancer prevention. We also describe the cases of cancer treatment with HAART drugs in HIV-negative people, including ongoing clinical studies that may directly point to a possible independent anti-oncogenic activity of HAART drugs. We conclude that despite potent antioncogenic activities of every class of HAART drugs reported in preclinical models, the evidence to date indicates that their independent clinical impact in HIV-infected people is limited. Improved cancer prevention strategies besides HAART are needed to reduce HIV-cancer-related mortality.

Introduction

The introduction of highly active antiretroviral therapy (HAART) in 1996 has profoundly modified the overall survival rates of people with HIV/AIDS. HAART suppresses viral replication, restores the immunity and reduces the mortality,[1] but even in the era of HAART, HIV-infected individuals still have a higher risk of developing cancer compared to healthy individuals. They also have a more severe clinical course of cancer and lower survival rate compared to the non-infected population.[2,3] In HIV+ patients, 10-20% of all deaths are attributable to cancer.[4,5]

Given the higher risks for HIV-positive population, developing cancer control strategies for this group is a rising challenge to public health. To provide the context for further research, we will discuss clinical aspects related to the cancer burden in patients with HIV-infection and highlight details on the role of antiretroviral drugs in the development of cancer, which is not limited to viral suppression. Preclinical studies have shown that many antiretroviral drugs could exert anti-tumor effects independently of their capacity to suppress viral replication and reconstitute the immune system. Understanding the role of HAART in HIV-cancer relationship is important to optimize cancer prevention strategies, screening and clinical management of people with HIV infection. The present review also discusses the clinical impact of antiretroviral treatment in terms of cancer.

Search strategy and selection criteria

The review is based on the works referenced in MEDLINE, EBSCO OpenDissertations, Cochrane Library, Web of Science, Scopus, Embase, ScienceDirect and Google scholar from January 1, 1996 to December 1, 2018. We also analyzed registers of clinical trials (Cochrane Central Register of Controlled Trials (CENTRAL); ClinicalTrials.gov), abstracts of scientific meetings related to cancer and reference lists of included studies relevant to the subject of the

review. The search terms were "highly active antiretroviral therapy", "HIV protease inhibitors", "HIV reverse transcriptase inhibitors", "CCR5 receptor antagonists", "HIV integrase inhibitors" and "cancer/neoplasms". The language of records was limited to English. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

HIV and cancer risks in the HAART era

HAART contributed to a slight reduction in overall cancer rates in HIV-infected people.[6–8] Nevertheless, nowadays people living with HIV still have a 1·6-1·7-fold greater overall risk of cancer development relative to the general population,[8,9] and the risk is rising with age.[10] This fact can be explained by predisposing factors such as immunosuppression combined with chronic inflammation due to virus persistence.[11,12] HIV-infected population is also more susceptible to cancer risk behavior (men who have sex with men, intravenous drug use, heavy alcohol consumption, smoking) than general population and is prone to frequent coinfection with other oncogenic viruses (Epstein Barr Virus (EBV), Human Herpesvirus Virus 8 (HHV-8), Human Papilloma Virus (HPV), Hepatitis B and C Viruses (HBV, HCV)) exacerbated by loss of immune control.[11,12] This results in a cumulative greater probability of cancer development. Some of these risk factors are modifiable. Highly active antiretroviral therapy (HAART) restores the immunity and suppresses viral replication,[1] it was also shown to possess preclinical antioncogenic activity, which will be discussed below (Fig. 1).

Prevalence of these risk factors among people with HIV infection indicates a vital need for risk factor reduction efforts,[13] including a possible pharmacological intervention. Indeed, a combination of HIV and cancer produces a synergistic effect on mortality rates, which become significantly higher than mortality rates for each disease taken separately.[3]

AIDS-defining cancers (ADCs: Kaposi's sarcoma, non-Hodgkin's lymphoma (NHL), invasive cervical cancer) are traditionally distinguished in HIV-infected patients; other cancers are

referred to as non-AIDS defining cancers (NADCs).[14] NADCs, in turn, are usually classified into virus-related cancers (HPV-, EBV-, HCV-related cancers) and virus-unrelated cancers.

ADCs

HAART contributed to a significant decline in the incidence of ADCs, the outcome of such cancers has improved and mortality has decreased.[8,15–18] However, the risks for developing all ADCs are still largely elevated in HIV-infected people; this risk is proportional to the HIV load and inversely proportional to the CD4 cell count (Fig. 1).[19,20] Immunosuppression is a strong predictor for ADCs. For Burkitt's lymphoma, albeit, immune reconstitution is supposed to be, at certain CD4 cell counts, a risk factor for the development of lymphoma, indicating a more complex relationship with the immune status.[21–23] Consistently, it was shown that the incidence of Burkitt's lymphoma is either rising in the HAART era,[24,25] or remains stable over time[9,23] as opposed to other NHLs; the proportion of Burkitt's lymphoma among NHLs is growing.[26]

NADCs

The number of all non-AIDS defining cancers (NADCs) is increasing since 1996 compared to the pre-HAART era and is expected to continue to rise.[27,28] Both virus-related and virus-unrelated cancers contribute to this trend.[29] NADCs represent approximately 2/3 of all cancers in HIV-patients; they are two times more frequent than ADCs.[9,11] The rise of NADCs in the HAART era is in part linked to the overall aging of people with HIV, this provides more time for cancer to evolve.[11,29] Contrary to ADCs, the association of risk of NADCs and CD4 counts or HIV load is still a matter of discussion, as some researchers suppose they are not related,[30] while others have shown that immunodeficiency was a risk factor associated with NADCs incidence.[31–34] It appears that low CD4 cell count is a specific risk factor exclusively for virus-related NADCs, but not for virus-unrelated ones,[34] e.g. CD4 counts are significantly higher in HIV+

patients that develop prostate cancer compared to HIV+ patients without cancer, indicating that lower CD4 counts are possibly associated with less prostate cancer risk.[35]

The overall incidence of NADCs in HIV-positive individuals was shown to be up to two times higher compared to the general population and it remains basically unchanged during the HAART era.[2,8,9] This elevated incidence is mainly due to virus-related NADCs, which are five times more frequent in HIV-infected people: Hepatitis B Virus (HBV)/HCV-related hepatocellular carcinoma, HPV-related oropharyngeal cancers, HPV-related anal cancer, EBV-related classical Hodgkin lymphoma, and others.[9] Some virus-unrelated NADCs: lung, larynx, nasal cavity cancers also occur more frequently in HIV-infected people;[9] this effect can be partially explained by the prevalence of smokers.[36,37] Smoking cessation should be discussed with patients to reduce cancer risk (Fig. 1).[38]

Interestingly, for some reasons, some cancers are significantly more rare in HIV-infected patients compared to the general population.[9] They include stomach, colorectal, kidney, uterus, prostate, breast, brain, thyroid cancers.[9,39–41] This cannot be solely explained by targeted cancer screening for these types of cancer (mammography, colon-/sigmoidoscopy, PSA test)[39] or hormone levels alteration due to HIV infection.[42] Overweight/obesity is less prevalent in people living with HIV than in general population, and that is a proposed risk factor for gastrointestinal tract tumors, breast, endometrial and renal cancers.[13,43] This requires further investigation with a direct comparison of HIV-infected people with body mass index-matched uninfected people. These trends may also be due to viral-host interaction. It is a common knowledge that HIV induces T-cell apoptosis.[44–46] Several studies have shown that HIV-1 and its molecules (gp120, Nef) can also mediate neuroblastoma,[47] breast,[48] colorectal,[49,50] prostate[51] cancer cell growth inhibition, and apoptosis. An interesting possibility, explaining lower frequency of several

cancers in HIV-infected persons, is that the HAART drugs can possess cancer-prevention or antineoplastic activity. Below we shall consider recent data on this subject.

HIV and cancer treatment in the HAART era

During the HAART era, cancer-contributable mortality is higher in patients with HIV compared to non-infected population even when clinical features are similar, and HIV-infected people diagnosed with cancer experience excess mortality that exceeds the expected mortality from a simple combination of HIV and cancer.[3,52–54] Cancer treatment in people living with HIV/AIDS is challenging due to the absence of clinical recommendations or established protocols and lack of clinical experience.[55] A significantly higher proportion of HIV-infected individuals does not receive treatment for diffuse large B-cell lymphoma, lung cancer, Hodgkin's lymphoma, prostate cancer, and colorectal cancer. HIV infection is associated with a lack of standard treatment modality for local-stage diffuse large B-cell lymphoma, non-small-cell lung cancer, and colon cancer.[55]

ADCs

The introduction of HAART has significantly improved survival rates for ADCs,[56] nevertheless, HIV infection seems to remain a factor increasing the risk of death in patients with ADCs. The overall survival of HIV-infected patients with NHLs and cervical cancer is significantly lower than in HIV-negative population.[57,58]

ADCs give better responses to treatment with the HAART + chemotherapy/radiotherapy combination rather than HAART alone or chemotherapy/radiotherapy alone,[59–63] therefore, HAART use is recommended for patients with ADCs.[14] No difference was found between PI-based HAART versus other regimens in treatment outcomes of Kaposi's sarcoma[64] and NHL[65,66] in a combination with chemotherapy. Even HAART treatment alone without chemotherapy can

lead to positive outcomes of Kaposi's sarcoma,[67–70] NHLs,[71–74] oncogenic cervical squamous intra-epithelial lesions.[75,76] Nonetheless, a further clinical study proved that HAART + chemotherapy combination gave a better response than HAART alone, albeit no difference in the survival rate was revealed.[77] At the same time, a PI-based regimen was revealed to be associated with higher toxicity during chemotherapy of lymphomas.[66] Patients with lymphomas receiving PI-based HAART had a significantly lower 1-year survival compared to NNRTI-based HAART probably due to toxicity.[78] Burkitt's lymphoma is again a puzzling exception among NHLs, since its outcome is still rather poor in the HAART era.[79,80]

NADCs

In the HAART era survival rates for HLs and anal cancer improved considerably.[56] The overall 3-year survival of HIV-infected patients with HLs is significantly lower than in HIV-negative population,[57] which might be due to treatment disparities.[81] For solid tumors, such as lung, liver, anal cancer five-year survival is comparable to that in general population.[56,82]

Promising results were obtained in several reports of NADCs treatment in HIV-infected people with HAART-drugs alone or in combination with chemotherapy, which resulted in a good clinical response.[83–87]

Combination of HAART and chemotherapy

HIV-infected people are generally excluded from clinical trials; therefore data on toxicity, outcomes and possible drug interactions during cancer treatment are limited. Despite the increased toxicity and drug-drug interactions, HAART withdrawal during chemotherapy is unfavorable in HIV-patients with cancer and can lead to a poorer outcome; [88] therefore in general, any HAART interruption is not advisable during cancer treatment.[38] Possible drug-drug interactions should be therefore carefully assessed when treating cancer in HIV-infected patients.

Drug-drug interactions rely on many factors, such as the route of elimination, the effect on enzymes and transporters involved in the drug metabolism. Both HAART and antioneoplastic drugs can be metabolized by CYP450 enzyme family and serve as CYP450 inhibitors, which can lead to drug accumulation and potential toxicity, or as CYP450 inducers, which leads to drug elimination and decreased efficacy, except for active metabolites of several drugs.[38,89] As an example, ritonavir*, a PI and a potent CYP3A4 inhibitor, was reported to be associated with more severe toxicity in combination with chemotherapy compared to non-ritonavir-based HAART.[88] On the contrary, NNRTIs are mainly CYP3A inducers.[89] HAART regimen should be modified when facing undesirable drug-drug interactions or elevated toxicity.[38] In this case, preference can be given to the INSTI-based regimen, which is supposed to be relatively safe.[38,90] Both NNRTIs and INSTIs are superior to PIs in terms of viral suppression in HIV-infected patients with malignancies.[90] Regarding the complexity of multidrug interaction, if a patient is HAART-naive, it is recommended to start HAART more than a week before or after the cancer treatment in order to differentiate between adverse effects.[38] It is also recommended that clinicians consult major reviews dedicated to the topic of potential drug-drug interactions between HAART and chemotherapeutic drugs,[89,91,92], treatment guidelines,[38] and refer to available resources such as http://www.hiv-druginteractions.org to optimize clinical management of HIV-infected patients with cancer and increase therapeutic benefit.

An individual pharmacogenetic profile is another factor that influences patients' response to drug combinations. A promising strategy is to evaluate personalized pharmacogenomic profile to predict efficacy and undesirable adverse effects of the therapeutic agents when planning HAART and chemotherapy regimens.[93]

* Ritonavir is currently recommended to improve the pharmacokinetic profiles of other antiretroviral drugs (pharmacokinetic booster), not as an independent HAART component.[94,198]

Thus, cancer treatment in people with HIV requires both an adequate control of HIV infection by HAART and an individual drug-drug interaction assessment.

HAART and cancer prevention

HAART is defined as the use of several (at least three, rarely two) antiretroviral drugs and has different regimens: two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third drug from one of three drug classes: HIV-integrase strand transfer inhibitors (INSTIs), non-nucleoside reverse transcriptase inhibitors (NNRTI), or HIV-protease inhibitors (PIs) are currently recommended.[94]

In HIV-infected people, HAART use is definitely associated with lower cancer incidence over no treatment for most cancers and particularly for ADCs.[7,95,96] Whether this effect is based on immune reconstitution and virus suppression, or it is an independent protective factor, remains unclear. HAART use is considered to be a strong factor responsible for the decreased ADCs occurrence in HIV-infected people and the greater cumulative exposure to HAART, the lower the risk of ADCs is.[97] The protective effect of HAART is mainly explained by virus inhibition and immune restoration. Although at first it was thought that HAART had an additional protective effect independent of CD4 cell count and viral load,[19,98–100] the latter studies did not detect any independent effect of HAART on Kaposi sarcoma incidence after adjusting for more variables and in a larger cohort.[20,101]

HAART was first reported to be protective for NADCs,[102] or to have no effect;[6] nowadays the use of HAART is associated with a higher rate of NADCs over no treatment and long cumulative exposure to HAART is a predictor of NADCs risk.[33,96,97,100] This effect is mainly driven by virus-related cancers, as their incidence was significantly higher in people treated with antiretrovirals compared to no antiretroviral treatment, while there was no change in virus-unrelated cancer rates between HIV-infected people with or without antiretroviral therapy.[100]

Improved survival of HIV-positive individuals during the HAART era may allow for sufficient time for virus-associated lesions to develop into malignancies. For Hodgkin's lymphoma, though, HAART use was not associated with higher cancer risk in large European cohort studies.[103–105] The absence of HAART was not proven to be an independent risk factor for NADCs.[19] HAART exposure did not play any role in lung cancer staging.[106] No association was shown between HAART use and the risk of lung cancer.[107,108] The opposite trend is observed in prostate cancer, where the cumulative antiretroviral exposure decreases cancer risk, though no difference was observed between people with or without antiretroviral therapy.[100] The role of HAART in anal cancer prevention is ambiguous. HAART is associated with a lower prevalence of anal intraepithelial neoplasia,[109] and it takes more time for anal cancer development in HAART era than before,[110] but treatment duration does not reduce anal cancer risk,[111] and HAART is considered to be a risk factor for relapse of anal cancer.[112]

A lack of specific and independent protective effect of HAART on cancer incidence, regardless of their potent antitumor effect observed in preclinical studies (see below), may be explained by low doses, sufficient for viral suppression, but insufficient for cancer prevention. These relationships are further complicated by various factors. For example, the hepatotoxicity of HAART may amplify the carcinogenic effect of HBV and HCV.[113] NRTIs, a mandatory component of main HAART regimens, were also considered to be genotoxic and carcinogenic.[114] However, large prospective cohort studies of HIV-negative children, perinatally exposed to any drug of NRTI class, revealed no change in cancer incidence compared to non-exposed ones and to the general population.[115–118] They found, albeit, that the risk of cancer development was significantly higher in those exposed to didanosine-lamivudine combination than to zidovudine monotherapy.[115] Later, it was found that didanosine exposure in HIV-negative children was oncogenic and accounted for higher cancer risk.[117,118] Didanosine use is not currently recommended.[94]

Comparison between HAART regimens in terms of cancer prevention

As HAART drugs have various mechanisms of action additionally to their main antiretroviral activity, their efficiency in cancer prevention can vary. Below we shall consider the association between HAART regimens and cancer risk.

ADCs

PI and NNRTI-based HAART were reported to have a similar protective effect on ADC incidence (Table 1).[97,100,119] Ritonavir-based, indinavir†-based or nelfinavir*-based therapy confers no advantages compared to other PI- or NNRTI-based regimens in the prevention of ADCs.[95,96,120] This is in line with the fact that the HAART impact on the decrease of ADCs is mainly connected with improvement in immune function and viral load.[20] At the same time, some studies showed potential advantages of PI-based HAART in ADCs prevention over other regimens. Only PI-containing HAART significantly reduces the frequency of HHV-8 detection compared to HAART-naïve patients.[121] In patients with low immune activity, PI-based therapy is more efficient at inducing complete response than NNRTI–HAART.[122] NNRTI-based HAART was shown to be associated with Kaposi's sarcoma relapse in a case series study (n = 5)[123] and in a small prospective cohort study (n = 45)[124], though the opposite was shown in another case series study (n = 24)[125]. NNRTIs were shown to be more potent in reducing the risk of NHL.[97] The regimens other than PI- or NNRTI-based are less studied, however, there were two case report of human herpesvirus 8 (HHV8) viremia and Kaposi's sarcoma relapse after switching from a PI- to an INSTI-based HAART and rapid remission of Kaposi's sarcoma after returning back to PI-based therapy.[126,127] A recent large cohort study found no evidence that INSTIs were

† Both indinavir and nelfinavir are no longer recommended accordingly to the latest guidelines of HIV treatement.[94]

associated with increased cancer risk.[128] Treatment with the CCR5 antagonist (vicriviroc‡) can be associated with the increased risk of developing cancers, including lymphomas,[129] but later studies showed that the cancer incidence was similar between vicriviroc and placebo;[130] maraviroc from the same class was also confirmed to be relatively safe.[131]

NADCs

Several large cohort studies reported no difference between PI- and NNRTI-based regimens in cancer prevention in all cancers except anal cancer (Table 1)[95,96,100,132]. One study showed NNRTI association with an increased risk of NADCs and precisely Hodgkin's lymphoma,[2] and controversially, another study showed that overall NADCs incidence was higher in people receiving PI-based HAART.[97] Moreover, the latter study reported that PI-based regimen did not decrease the risk of Hodgkin lymphoma, while NNRTI-based HAART did.[97]

PI-based HAART may be associated with an increased risk of anal cancer, whereas NNRTI use has no association with anal cancer or is associated with a decreased risk.[96,97,100,133,134] Interestingly, nelfinavir-based HAART was not associated with a higher risk of anal cancer as opposed to other PI-based regimens.[96] It was recently reported that adjustment for both CD4 cell count and cumulative NRTI exposure abolished the association of PI-based regimen with anal cancer risk in a case-control study.[135] On the other hand, PI use was associated with a lower risk of prostate cancer,[100] which is consistent with the overall lower incidence of prostate cancer in HIV-infected people compared to the general population. These trends remain difficult to explain.

In conclusion, currently there is no evidence for any particular HAART regimen being more or less associated with cancer risk for ADCs and virus-unrelated NADCs, except for a lower risk of

‡ Phase III clinical trials were discontinued and vicriviroc was not approved for HIV treatment.[94,198]

prostate cancer with a PI-based HAART. Regarding virus-unrelated NADCs, PI-based HAART is estimated to be associated with an increased risk of anal cancer and probably of Hodgkin lymphoma.

Preclinical antineoplastic activity of HAART drugs

Recent preclinical studies showed that HAART drugs from different classes possessed potent anti-oncogenic activity. The proposed mechanisms of their action are summarized in Fig. 2.

HIV-protease inhibitors (PIs) have pleiotropic pharmacological properties besides their antiretroviral activity. They have been reported to inhibit the growth of various cancer cell lines *in vitro* as well as tumors in *in vivo* xenografts models.[136–139] PIs induce cell growth arrest, endoplasmic reticulum stress, caspase-dependent apoptosis, autophagy (for review see [140–142]). Moreover, PIs are known for their anti-angiogenic and radiosensitizing effects.[141,143] PIs action is associated with inhibition of phosphatidylinositol 3-kinase (PI3K)/Akt pathway; one of the possible mechanisms is binding to Hsp90 and inhibiting its chaperone function followed by decreased PI3K/Akt signaling.[137,138] Together and independently of each other, PI3K and its downstream kinase Akt regulate various cell processes such as growth, proliferation, survival, migration, apoptosis; and their hyperactivation is a cancer hallmark.[144,145] PI3K/Akt signaling in cancer inhibits apoptotic enzymes; promotes activation of mTOR and NF-κB axes that regulate transcription, increase cell growth, survival, proliferation, increase matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) expression, associated with migration and angiogenesis, respectively; causes chemo-/radiotherapy resistance by misregulation of DNA damage response.[143,146–149] Akt, VEGF, MMPs and other important cancer-phenotype proteins are partners of Hsp90, the latter works as a molecular chaperone and guarantees correct folding of its substrates.[150] Hsp90 inhibition leads not only to targeted destabilization of key oncogenic

proteins but also to misfolded protein aggregation, endoplasmic reticulum stress, and apoptotic death or autophagy.[151,152]

Detailed docking analysis has shown that PIs can be potent Hsp90 inhibitors; their binding capacity to Hsp90 decreases in the following order: Nelfinavir, Indinavir, Saquinavir, Ritonavir, Lopinavir, Tipranavir, Darunavir, Amprenavir§.[153] Indeed, among all PIs, nelfinavir seems to have the highest anti-cancer activity.[141] It is noteworthy that a longitudinal study of antitumor effects of PIs and especially, nelfinavir, is nuanced by the fact that in 2007 Roche's Viracept (nelfinavir mesylate) was discovered to be contaminated by a mutagenic compound.[154] Importantly, PIs can also directly inhibit the replication of human herpesvirus 8 (HHV8), the etiological agent of Kaposi's sarcoma.[121,155]

Though at first nucleoside reverse transcriptase inhibitors (NRTIs) were supposed to be genotoxic, mutagenic and oncogenic due to their ability to incorporate into nuclear DNA and directly inhibit cellular DNA polymerases,[114,117,156,157] the subsequent clinical studies have shown no clear correlation between NRTIs and cancer (see above). In fact, *in vitro* studies have shown, that NRTIs might also possess anticancer activity,[158–160] which is probably associated with their capacity to inhibit DNA repair,[161] induce mitochondrial toxicity,[162] apoptosis, modulate activity and expression of endogenous reverse transcriptase encoded by the long interspersed nuclear element-1 (LINE-1).[158] LINE-1 propagation throughout the DNA may play a role in genome instability, mutagenesis and contribute to carcinogenesis.[163]

Another HAART class, non-nucleoside reverse transcriptase inhibitors (NNRTIs) were also demonstrated to inhibit the growth of cancer cell lines and xenografts in rodents,[157,164–166] among them, efavirenz is supposed to have the highest anticancer potential.[167] NNRTIs can act on cancer cells through the induction of DNA damage,[157] apoptosis,[168] oxidative stress,[165] and

§ Amprenavir production was discontinued, a prodrug fosamprenavir is available and approved.[94,198]

downregulation of LINE-1 expression.[169] Similarly to PIs, exposure to NNRTIs was associated with the radiosensitizing effect.[165,170]

HIV-integrase strand transfer inhibitors (INSTIs) may cause aberrant HIV-integration and rearrangements in the host DNA when used in low doses.[171,172] Low-dose INSTI may create the situation when strand transfer reaction is blocked at only one of two ends of viral DNA, which subsequently leads to mutation-prone integration of a blocked end *via* the host enzymes.[171] Thus, these drugs are potentially mutagenic and carcinogenic; however, there is no evidence for increased cancer risk in patients exposed to INSTIs. INSTIs were also shown to inhibit a metnase enzyme associated with chemotherapy resistance;[173] thus they can be potentially applied together with antineoplastic drugs to increase their efficacy.

Finally, recent studies have shown that CCR5 antagonists are also potent antioncogenic and antimetastatic effectors for various cancer cell lines and xenografts.[174–178] CCR5 blockade results in a decreased invasion, migration, metastatic potential cell proliferation, and leads to proapoptotic signaling.[174,176,179]

Thus, the preclinical data on HAART components point to its protective effect against cancer for virtually every class of drug, which is very promising in terms of drug repositioning. Still, it is important to reveal the causal impact of these drugs on humans who undergo HIV and/or cancer treatment.

Antiretroviral drugs and cancer treatment in HIV-negative patients

As many *in vitro* studies have shown the anticancer activity of HAART drugs, they were proposed for use in cancer treatment. In addition, the use of antiretroviral drugs in HIV-negative people with cancer can help us evaluate a possible protective effect of HAART, independent of its antiretroviral activity *per se*. The favorable treatment outcome of HIV-negative patients with

Kaposi's sarcoma treated with indinavir (PI) points to its direct antioncogenic properties in ADCs.[180] At present, several clinical trials of antiretroviral drugs in cancer are underway. They are summarized in Table 2. However, the data addressing this question are still limited, and the results obtained from clinical trials are often inconclusive.

Promising results were obtained for nelfinavir (PI) as monotherapy or combined with chemoradiotherapy in phase I clinical trials: in locally advanced pancreatic cancer,[181] in locally advanced non-small cell lung cancer,[182] in locally advanced rectal cancer,[183] in multiple myeloma,[184] in neuroendocrine tumors of the midgut or pancreatic origin,[185] and in glioblastoma multiforme,[186] where the level of response was higher than reported before and the toxicity was acceptable. A phase II clinical trial of nelfinavir added to bortezomib and dexamethasone in the proteasome inhibitor-refractory multiple myeloma showed exceptional response rates (~65%).[184] A phase II clinical trial of nelfinavir combined with chemoradiation in locally advanced inoperable pancreatic cancer showed improved tumor oxygenation and perfusion, which might lead to better treatment response, however, the study was discontinued because of the unavailability of nelfinavir in Europe.[187] Data from a phase I clinical trial of maraviroc (CCR5 antagonist) in advanced colorectal cancer with hepatic metastases showed a partial response in patients with previously refractory disease.[179] Lopinavir/Ritonavir combination (PIs) was successfully used for the treatment of HPV-positive high grade squamous intraepithelial lesions in HIV-negative women.[188] There was also a case report of successful thyroid papillary carcinoma treatment with a combination of Nevirapine (NNRTI) and radioiodine, resulting in re-induction of cell differentiation, better drug uptake and sensitivity to treatment, slower progression of the disease.[189,190] However, definite conclusions cannot be drawn at this stage due to a small number of patients, possible patient selection bias, and lack of control groups.

Some studies point to the absence of the anti-tumor activity of antiretroviral drugs. No meaningful improvement in clinical outcomes was reported among patients with recurrent adenoid cystic carcinomas and nelfinavir (PI) monotherapy in a phase II clinical trial.[191] The use of efavirenz (NNRTI) also did not improve the non-progression rate of castration-resistant prostate cancer in a phase II clinical trial.[192] A phase II clinical trial of ritonavir/lopinavir (PIs) combination in patients with progressive or recurrent high-grade gliomas did not reveal a potent clinical activity either.[193] These results can be explained by low effectivity of these drugs as monotherapy, by low plasma concentrations of drugs, or their low tissue concentrations due to poor access to the tumor. Therefore, even though some results concerning the use of antiretroviral drugs in cancer treatment are promising, further studies, investigating higher dosage of the drugs and combinations with chemoradiotherapy, are necessary to assess their effectiveness in the treatment of different types of cancer and will provide insight into optimal oncological doses of HAART drugs.

Conclusions

HIV-associated cancers are a serious health problem leading to rising mortality in an HIV-infected population, therefore cancer prevention and cancer control strategies are required. The main trends in cancer incidence relative to HAART treatment are summarized in Table 3. The main protective effect of HAART in HIV-infected people is related to ADCs and may be explained by immune reconstitution and viral suppression. The effect of HAART in NADCs is more complex and nuanced. Interestingly, the difference between HAART regimens in cancer prevention is observed only for virus-related cancers, where PI-based HAART is less favorable than other regimens. The role of HAART during cancer treatment is positive, though it may be complicated by drug-drug interactions. The later should be carefully assessed by clinicians when planning the cancer treatment in HIV-infected people. Doctors should also take measures to

reduce risk behavior in people with HIV (smoking and alcohol consumption cessation), as a cancer prevention strategy and during cancer treatment. PI-based HAART is not preferred during cancer treatment as well, because of suboptimal viral suppression in patients with HIV and cancer.

Antiretroviral drugs that are in use since many years were recently shown to be potentially antineoplastic and therefore may present an elegant solution for cancer control in this population. The plethora of published articles studied their effects in primary cells, tumor cell lines, and tumor xenografts models, however, their effect on cancer prevention, treatment and outcome in humans remains poorly understood. Here, we summarized and discussed all potential clinical aspects related to the impact of antiretroviral treatment on cancer.

Finally, several reports of HAART use in cancer treatment in the HIV-negative population may help answer the question about an antioncogenic activity of HAART, but to date, the data from clinical studies are still limited. It is possible that some modifications or optimizations of HAART regimens are required in order to observe antioncogenic and cancer-protective properties of these drugs in clinical practice.

Many epidemiological studies exploring HIV-cancer relationships have a common limitation: they lack the information on antiretroviral therapy, thus a potentially promising question about the relationships between HAART and cancer risks and outcomes remains unanswered. The absence of clinical recommendations, together with a lack of experience regarding cancer prevention or simultaneous treatment of HIV and cancer and substandard cancer care, indicates an urgent need for large-scale epidemiological studies addressing the question about the effect of particular HAART drugs and their dosage on cancer prevention. Furthermore, inclusion of people with HIV in clinical trials of antineoplastic treatments should be encouraged.

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Appendixes

Tables

Table 1. A comparison of regimens based on non-nucleoside reverse transcriptase inhibitors, protease inhibitors or integrase strand transfer inhibitors in preventing cancers in HIV-infected persons.

Type of cancer	Study design	Cohort size	Conclusion	Reference
ADCs				
ADCs, Kaposi's sarcoma alone, NHL alone	Prospective cohort study	42006	Nelfinavir = non-Nelfinavir-PI = NNRTI in cancer prevention	96
ADCs, Kaposi's sarcoma alone	Prospective cohort study	41762	PI = NNRTI in cancer prevention	97
NHL alone			NNRTI, but not PI, is associated with a lower risk	
Kaposi's sarcoma	Prospective cohort study	4480	Ritonavir = non-Ritonavir-PI = NNRTI in cancer prevention	120
Kaposi's sarcoma	Prospective cohort study	1204	PI = NNRTI in cancer prevention	119
Kaposi's sarcoma	Prospective cohort study	45	Kaposi's sarcoma relapse after switch from PI to NNRTI	124
ADCs, Kaposi's sarcoma alone, NHL alone	Retrospective cohort study	12872	PI = NNRTI in cancer prevention	100
ADCs	Retrospective cohort study	2499	Nelfinavir = Indinavir = other regimens in cancer prevention	95
Kaposi's sarcoma	Retrospective cohort study	91	PI = NNRTI in cancer incidence and clinical course	194
Kaposi's sarcoma	Case series	24	No Kaposi's sarcoma relapse after switching from PI to NNRTI	125
Kaposi's sarcoma	Case series	5	Kaposi's sarcoma relapse after switch from PI to NNRTI	123
Kaposi's sarcoma	Case report	1	PI switch to INSTI leaded to HHV8 viremia and sarcoma relapse	127
Kaposi's sarcoma	Case report	1	PI switch to INSTI led to HHV8 viremia, while INSTI switch back to PI resulted in a remission	126
NADCs				
Anal cancer	Prospective cohort study	72355	PI monotherapy, opposite to other antiretroviral therapy, is associated with increased cancer risk	134

NADCs, anal cancer alone	Prospective cohort study	42006	PI = NNRTI in cancer prevention, except for a higher risk of anal cancer with longer non-Nelfinavir PI, but not Nelfinavir or NNRTI	96
NADCs, anal cancer alone, HL alone	Prospective cohort study	41762	PI but not NNRTI, use is associated with increased cancer risk	97
Lung cancer, head and neck cancers			PI = NNRTI in cancer prevention	
NADCs, HL alone	Prospective cohort study	5076	NNRTI but not PI or NRTI therapy was associated with an increased risk of NADCs	2
NADCs	Prospective cohort study	3158	Initial PI = NNRTI = NRTI in cancer prevention	132
Virus-related, virus-unrelated NADCs	Retrospective cohort study	12872	PI = NNRTI in cancer prevention, except for a higher risk of anal cancer with longer PI, but not NNRTI	100
NADCs	Retrospective cohort study	2499	Nelfinavir = Indinavir = other regimens in cancer prevention	95
All cancers				
All cancers	Prospective cohort study	7971	Raltegravir (INSTI) is not associated with an increased risk of cancer compared with other treatment strategies	128

Abbreviations: INSTI, HIV-integrase strand transfer inhibitor-based antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy; PI, HIV-protease inhibitor-based antiretroviral therapy.

Table 2. Clinical trials of antiretroviral drugs in non-HIV related cancer treatment.

NCT number	Drug	Condition	Phase	Actual enrollment	Start date
HIV-protease inhibitors					
NCT00233948	Nelfinavir	Liposarcoma	I/II	29	March 2006
NCT01445106	Nelfinavir	Solid Tumors	I	28	December 2006
NCT00589056	Nelfinavir	Stage III Non-Small Cell Lung Cancer	I/II	55	June 2007
NCT01068327	Nelfinavir	Locally Advanced Pancreatic Cancer	I	46	November 2007
NCT00704600	Nelfinavir	Rectal Cancer	I/II	15	September 2008
NCT00694837	Nelfinavir	Glioblastoma	I/II	6	March 2009
NCT00915694	Nelfinavir	Glioblastoma Multiforme	I	23	April 2009
NCT01020292	Nelfinavir	Grade IV Glioma	I	31	April 2009
NCT01086332	Nelfinavir	Pancreatic Cancer	I	7	May 2009
NCT01079286	Nelfinavir	Advanced Cancers	I	18	June 2009

NCT01065844	Nelfinavir	Adenoid Cystic Cancer of the Head and Neck	II	15	October 2009
NCT01108666	Nelfinavir	Inoperable Stage III Non Small Cell Lung Cancer	I	72	March 2010
NCT01164709	Nelfinavir	Relapsed or Progressive Advanced Hematologic Cancer	I	18	July 2010
NCT01485731	Nelfinavir	Cervical Cancer	I	8	January 2012
NCT01555281	Nelfinavir	Progressive Multiple Myeloma	I/II	33	February 2012
NCT01925378	Nelfinavir	Cervical Intraepithelial Neoplasia	II	10	July 2012
NCT01728779	Nelfinavir	Oligometastases	II	40	June 2013
NCT01959672	Nelfinavir	Locally Advanced Pancreatic Cancer	II	12	September 2013
NCT02207439	Nelfinavir	Squamous Cell Carcinoma of the Oral Cavity, Oropharynx, Larynx, or Hypopharynx	II	28	July 2014
NCT02188537	Nelfinavir	Proteasome Inhibitor-nonresponsive Myeloma	II	34	December 2014
NCT02363829	Nelfinavir	Locally Advanced Cervical Cancer	I	6	February 2015
NCT02024009	Nelfinavir	Advanced Localised Pancreatic Cancer	I/II	289	March 2016
NCT03050060	Nelfinavir	Advanced Melanoma, Lung, or Kidney Cancer	II	120	June 2017
NCT03256916	Nelfinavir	Locally Advanced Carcinoma of Cervix	III	0	September 2017
NCT00637637	Ritonavir / Indinavir	Brain Metastases	II	60	September 2007
NCT01095094	Ritonavir / Lopinavir	Progressive or Recurrent High-Grade Glioma	II	19	January 2009
NCT01009437	Ritonavir	Breast Cancer	I/II	28	May 2010
NCT03066154	ModraDoc006/r (oral docetaxel with ritonavir)	High-risk Prostate Cancer	I	24	September 2016
NCT02770378	Ritonavir	Recurrent Glioblastoma	I	10	November 2016
NCT03136640	ModraDoc006/r (oral docetaxel with ritonavir)	Castration-resistant Prostate Cancer	I	20	April 2017
NCT03150368	ModraDoc006/r (oral	Advanced Solid Tumors	I	22	May 2017

	docetaxel with ritonavir)				
NCT03383692	Ritonavir	Advanced Solid Malignant Tumors	I	40	January 2018
Nucleoside reverse transcriptase inhibitors					
NCT03144804	Lamivudine	p53 Mutant Metastatic Colorectal Cancer	II	32	October 2017
Non-nucleoside reverse transcriptase inhibitors					
NCT00964002	Efavirenz	Metastatic Prostate Cancer	II	60	May 2008
NCT00964171	Efavirenz	Metastatic Pancreatic Cancer	II	72	August 2008
NCT01878890	Efavirenz	Solid Tumours or NHL	I	30	June 2011
Integrase strand transfer inhibitors					
NCT01275183	Raltegravir	Squamous Cell Carcinoma of Head and Neck	I	5	December 2010
CCR5 antagonist					
NCT01736813	Maraviroc	Metastatic Colorectal Cancer	I	12	November 2012
NCT03274804	Maraviroc	Metastatic Colorectal Cancer	I	20	April 2018

The studies on AIDS-, EBV-, HBV-, HCV-, HTLV-related cancers are excluded.

Table 3. Summary of the role of HAART in HIV-cancer relationship.

Parameter	All cancers	ADCs	NADCs	
			Virus-related	Virus-unrelated
Cancer incidence compared to the general population in the pre-HAART era	↑↑	↑↑↑	↑	= *
Cancer incidence compared to the general population in the HAART era	↑	↑↑	↑	↓
Cancer incidence in the HAART era compared to the pre-HAART era	↓	↓↓↓**	↑	↑
The risk of cancer with HAART use compared to no treatment	↓	↓↓↓	↑	=

* – due to a small cohort size and a large 95%-confidence interval

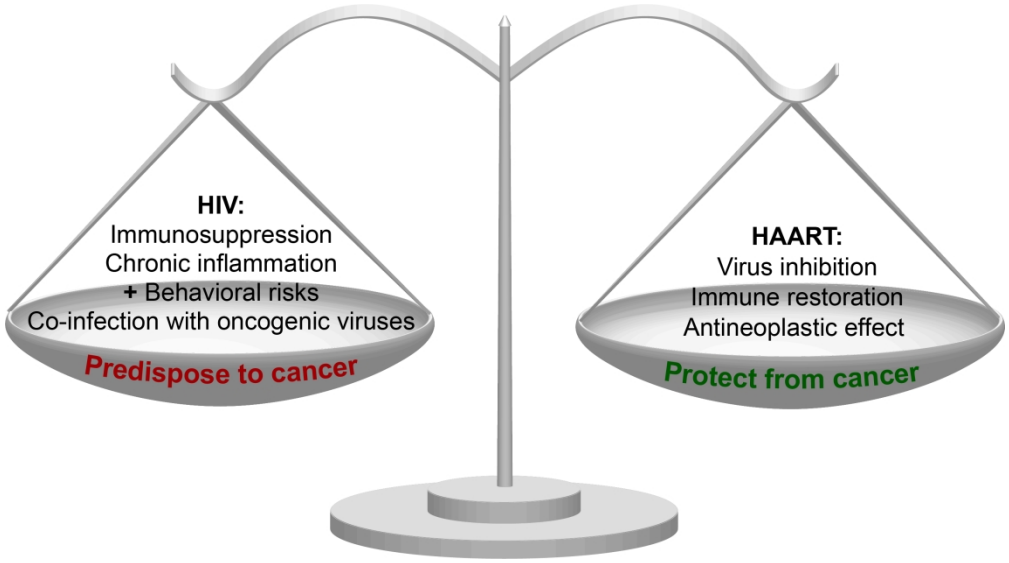
** – except Burkitt's lymphoma;

Sources:[195,196] and other articles cited in the text.

Figure legends

Figure 1. Factors influencing the risk of cancer in HIV-infected people. Cancer risk factors are represented on the left. Immunosuppression and chronic inflammation, caused by HIV infection, predispose to tumorigenesis. Besides, HIV-infected population is more susceptible to cancer risk behavior (smoking, men who have sex with men, intravenous drug use, alcohol consumption) and coinfection with other oncogenic viruses. Some of these risk factors are modifiable. Factors that reduce cancer risk are represented on the right. Highly active antiretroviral therapy (HAART) restores the immunity and suppresses viral replication, it was also shown to possess preclinical antioncogenic activity; however, the clinical relevance of this activity remains to be elucidated.

Figure 2. Potential mechanisms of the antineoplastic effects of different classes of HAART drugs. A. PI3K/Akt pathway regulates growth, proliferation, survival, migration, and apoptosis. In cancer, PI3K/Akt activation inhibits apoptotic enzymes; promotes transcription regulation that increases growth, survival, proliferation, increases MMPs (migration, invasion, metastasis) and VEGF (angiogenesis) expression *via* mTOR and NF-κB axes; causes chemo-/radiotherapy resistance by deregulation of DNA damage response. **PIs** inhibit the PI3K/Akt pathway, possibly through binding to Hsp90 and inhibiting its chaperone function. MMPs and VEGF are also Hsp90 clients destabilized by chaperone inhibition; overall, Hsp90 inhibition leads to misfolded protein aggregation, ER stress, apoptosis, and autophagy. CCR5 receptor promotes pro-oncogenic cascades as it also activates the PI3K/Akt pathway, thus **CCR5 antagonists** are also antioncogenic effectors. Other pathways implicated in CCR5 downstream signaling include phospholipase C-γ, Rac/CDC42/RhoA, JAK-STAT pathways (data not shown)[197]. **B. NRTIs** and **NNRTIs** interfere with nuclear DNA integrity, mitochondrial DNA maintenance and oxidative stress, retrotransposon LINE-1 expansion, which makes them potential anticancer agents. LINE-1 promotes genome instability and contributes to carcinogenesis. **INSTIs** also inhibit the DNA-repair enzyme metnase involved in chemotherapy resistance. Abbreviations: CCR5, C-C chemokine receptor type 5; ER, endoplasmic reticulum; INSTI, HIV-integrase strand transfer inhibitor; LINE-1, long interspersed nuclear element-1; MMPs, matrix metalloproteinases; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, HIV-protease inhibitor; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; RT, reverse transcriptase; VEGF, vascular endothelial growth factor. ➤ - promoting downstream effect, ⊣ - inhibiting downstream effect, ▬▬ - active pathway under the action of drugs, ▪ ▪ ▪ - suppressed pathway under the action of drugs, ↳ - gene transcription, ⇧ and ⇩ - resulting effects of drugs on critical cellular cancer-related processes (activation and suppression, respectively).



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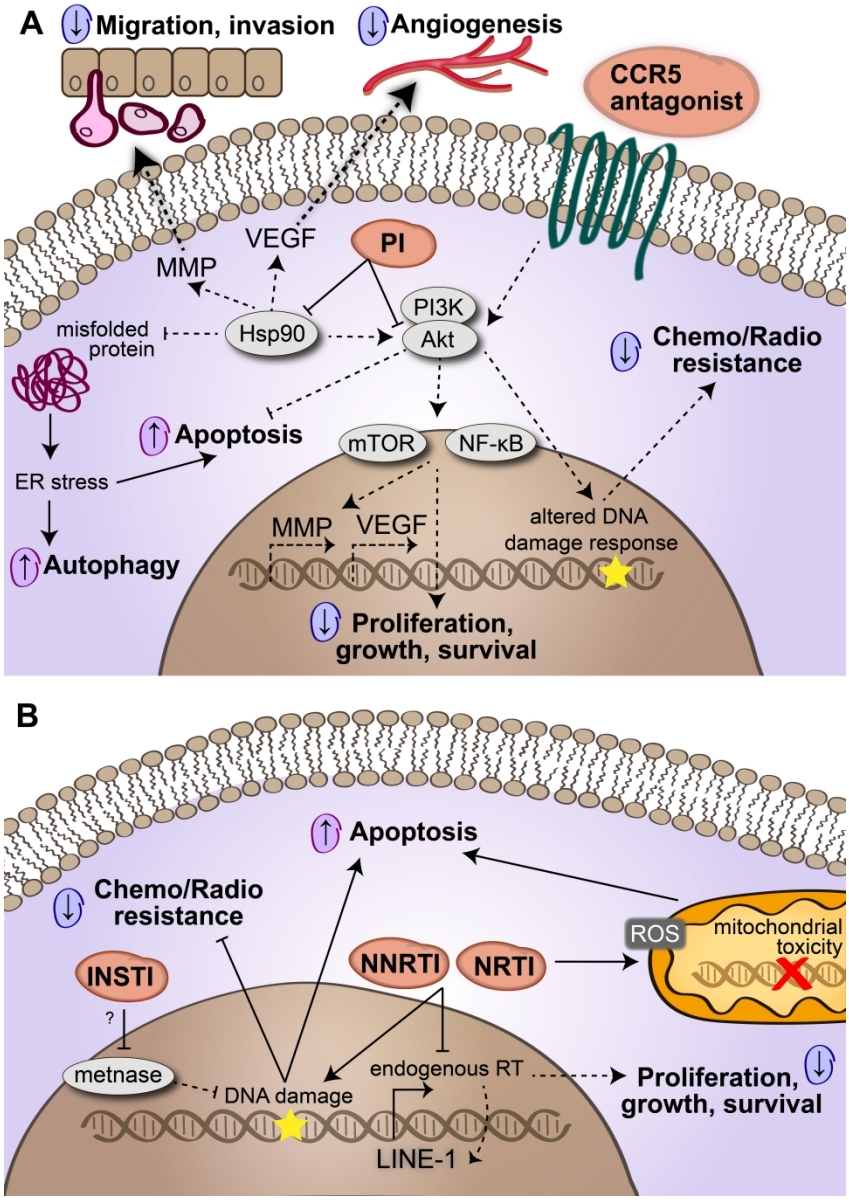

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