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HIV-1, HAART and cancer: A complex relationship

Anna Shmakova [1,2,3], Diego Germini [1,2] and Yegor Vassetzky [1,2,4]

[1]UMR 8126, CNRS, Univ. Paris-Sud, Institut Gustave Roussy, Université Paris Saclay, Édouard-Vaillant, Villejuif, France
[2]LIA 1066 LFR2O French-Russian Joint Cancer Research Laboratory, Édouard-Vaillant, Villejuif, France
[3]Laboratory of Gene and Cell Technologies, Faculty of Medicine, Lomonosov Moscow State University, Moscow, Russia
[4]Koltzov Institute of Developmental Biology, Moscow, Russia

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 causes 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 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 noninfected population.[2,3] In HIV+ patients, 10–20% of all deaths are attributable to cancer.[4,5]

Key words: HIV-1, AIDS, cancer, HAART, anticancer drugs

Abbreviations: AIDS: acquired immune deficiency syndrome; CCR5: C-C chemokine receptor type 5; EBV: Epstein–Barr virus; HAART: highly active antiretroviral therapy; HBV: hepatitis B virus; HCV: hepatitis C virus; HHV: human herpes virus; HIV: human immunodeficiency virus; HPV: human papillomavirus; 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

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Correspondence to: Dr Yegor Vassetzky, E-mail: yegor.vassetzky@cnrs.fr

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 antitumor 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 and 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- and HCV-related cancers) and virus-unrelated cancers.

AIDS-defining cancers

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]

Non-AIDS defining cancers

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 remains 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

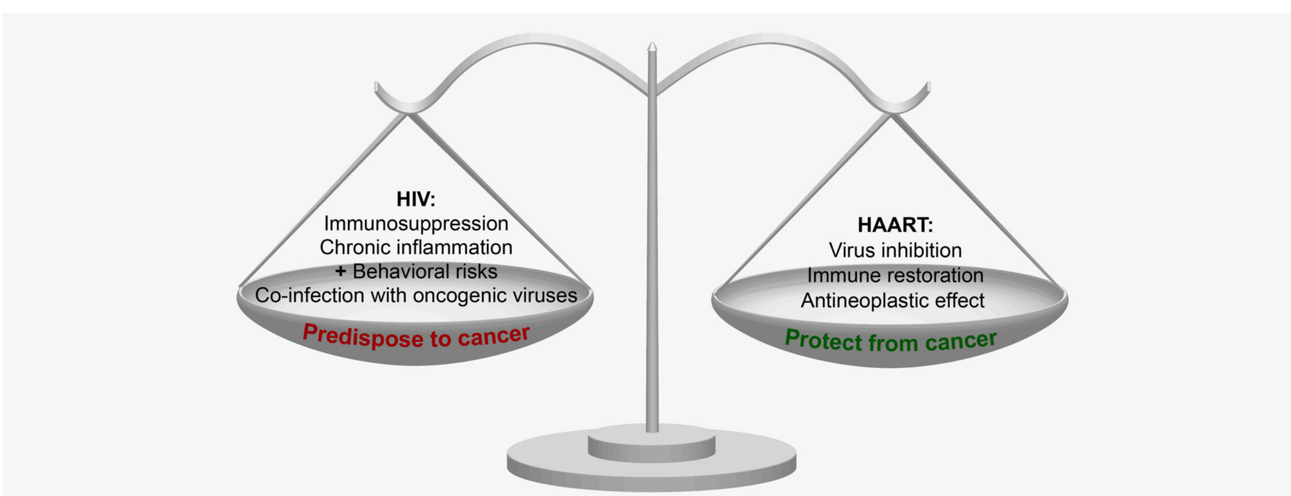

Figure 1. Factors influencing the risk of cancer in HIV-infected people. Cancer risk factors are represented on the left. Immunosuppression and chronic inflammation, caused by HIV infection, predispose to tumorigenesis. Besides, HIV-infected population is more susceptible to cancer risk behavior (smoking, 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. [Color figure can be viewed at wileyonlinelibrary.com]

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not for virus-unrelated ones,[34] for example, 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 and 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 noninfected 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, nonsmall-cell lung cancer and colon cancer.[55]

AIDS-defining cancers

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 *vs.* 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 intraepithelial 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 remains rather poor in the HAART era.[79,80]

Non-AIDS defining cancers

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 5-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 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 nonritonavir-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]

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 nonexposed 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

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

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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.

AIDS-defining cancers

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 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]

Non-AIDS defining cancers

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 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 antioncogenic activity. The proposed mechanisms of their action are summarized in Figure 2.

HIV-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 antiangiogenic 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

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

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

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	References
ADCs				
ADCs, Kaposi's sarcoma alone, NHL alone	Prospective cohort study	42,006	Nelfinavir = non-Nelfinavir-PI = NNRTI in cancer prevention	96
ADCs, Kaposi's sarcoma alone	Prospective cohort study	41,762	PI = NNRTI in cancer prevention	97
NHL alone			NNRTI, but not PI, is associated with a lower risk	
Kaposi's sarcoma	Prospective cohort study	4,480	Ritonavir = non-Ritonavir-PI = NNRTI in cancer prevention	120
Kaposi's sarcoma	Prospective cohort study	1,204	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	12,872	PI = NNRTI in cancer prevention	100
ADCs	Retrospective cohort study	2,499	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	72,355	PI monotherapy, opposite to other antiretroviral therapy, is associated with increased cancer risk	134
NADCs, anal cancer alone	Prospective cohort study	42,006	PI = NNRTI in cancer prevention, except for 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	41,762	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	5,076	NNRTI but not PI or NRTI therapy was associated with an increased risk of NADCs	2
NADCs	Prospective cohort study	3,158	Initial PI = NNRTI = NRTI in cancer prevention	132
Virus-related, virus-unrelated NADCs	Retrospective cohort study	12,872	PI = NNRTI in cancer prevention, except for higher risk of anal cancer with longer PI, but not NNRTI	100
NADCs	Retrospective cohort study	2,499	Nelfinavir = Indinavir = other regimens in cancer prevention	95
All cancers				
All cancers	Prospective cohort study	7,971	Raltegravir (INSTI) is not associated with an increased risk of cancer compared to 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.

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 and Amprenavir[§].[153] Indeed, among all PIs, nelfinavir seems to have the highest anticancer 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 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

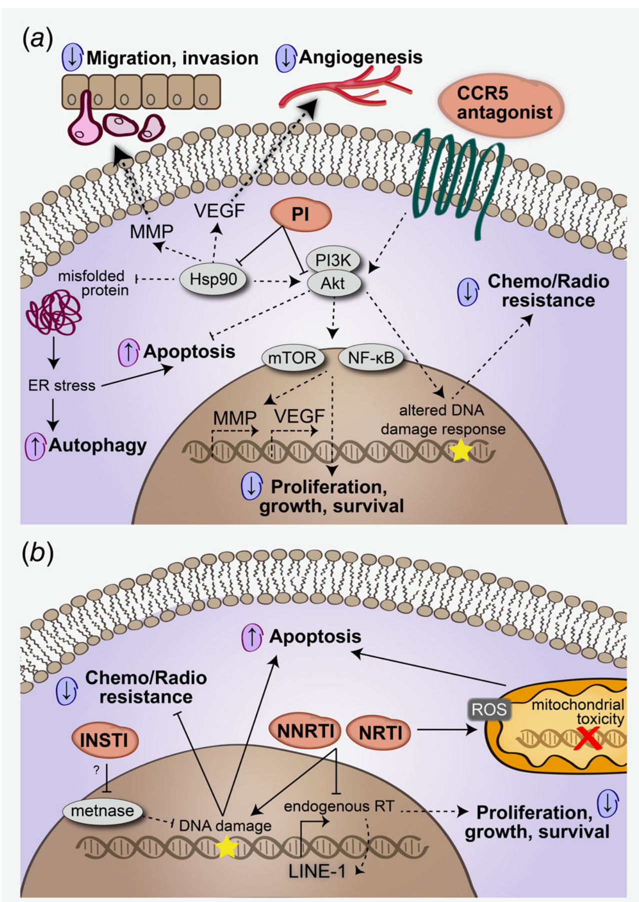

Figure 2. Legend on next column.

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 and 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 menace 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; ↑↓—resulting effects of drugs on critical cellular cancer-related processes (activation and suppression, respectively). [Color figure can be viewed at wileyonlinelibrary.com]

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

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 Nonsmall 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 Nonsmall 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 Localized 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 docetaxel with ritonavir)	Advanced Solid Tumors	I	22	May 2017
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 Tumors or NHL	I	30	June 2011
Integrase strand transfer inhibitors					

(Continues)

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

NCT number	Drug	Condition	Phase	Actual enrollment	Start date
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- and HTLV-related cancers are excluded.

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 nonsmall 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

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	↑↑	↑↑↑	↑	=[1]
Cancer incidence compared to the general population in the HAART era	↑	↑↑	↑	↓
Cancer incidence in the HAART era compared to the pre-HAART era	↓	↓↓↓[2]	↑	↑
The risk of cancer with HAART use compared to no treatment	↓	↓↓↓	↑	=

Sources[195,196]: and other articles cited in the text.
[1]Due to a small cohort size and a large 95% confidence interval.
[2]Except Burkitt's lymphoma.

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 antitumor 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 nonprogression 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 for 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, the inclusion of people with HIV in clinical trials of antineoplastic treatments should be encouraged.

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References

1. HIV-CAUSAL Collaboration, Ray M, Logan R, et al. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. *AIDS* 2010;24:123–37.
2. Powles T, Robinson D, Stebbing J, et al. Highly active antiretroviral therapy and the incidence of non–AIDS-defining cancers in people with HIV infection. *J Clin Oncol* 2009;27:884–90.
3. Coghill AE, Shiels MS, Suneja G, et al. Elevated cancer-specific mortality among HIV-infected patients in the United States. *J Clin Oncol* 2015;33: 2376–83.
4. Engels EA, Yanik EL, Wheeler W, et al. Cancer-attributable mortality among people with treated human immunodeficiency virus infection in North America. 2017;65:636–43.
5. Goehringer F, Bonnet F, Salmon D, et al. Causes of death in HIV-infected individuals with immunovirologic success in a National Prospective Survey. *AIDS Res Hum Retroviruses* 2017;33: 187–93.
6. Crum-Cianflone N, Hullsiek KH, Marconi V, et al. Trends in the incidence of cancers among HIV-infected persons and the impact of antiretroviral therapy: a 20-year cohort study. *AIDS* 2009;23:41–50.
7. Franceschi S, Lise M, Clifford GM, et al. Swiss HIV cohort Study the SHC. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV cohort Study. *Br J Cancer* 2010;103:416–22.
8. Park LS, Tate JP, Sigel K, et al. Time trends in cancer incidence in persons living with HIV/AIDS in the antiretroviral therapy era: 1997-2012. *AIDS* 2016;30: 1795–806.

Review

9. Hernández-Ramírez RU, Shiels MS, Dubrow R, et al. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. *Lancet HIV* 2017;4: e495–504.
10. Hasse B, Ledergerber B, Furrer H, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort Study. *Clin Infect Dis* 2011;53: 1130–9.
11. Robbins HA, Pfeiffer RM, Shiels MS, et al. Excess cancers among HIV-infected people in the United States. *JNCI J Natl Cancer Inst* 2015; 107:dju503.
12. Hart BB, Nordell AD, Okulicz JF, et al. INSIGHT SMART and ESPRIT groups. Inflammation related morbidity and mortality among HIV-positive adults. JAIDS. *J Acquir Immune Defic Syndr* 2017;77:1.
13. Park LS, Hernández-Ramírez RU, Silverberg MJ, et al. Prevalence of non-HIV cancer risk factors in persons living with HIV/AIDS: a meta-analysis. *AIDS* 2016;30:273–91.
14. Berretta M, Di Francia R, Stanzione B, et al. New treatment strategies for HIV-positive cancer patients undergoing antiblastic chemotherapy. *Expert Opin Pharmacother* 2016;17:2391–403.
15. Franceschi S, Maso LD, Rickenbach M, et al. Kaposi sarcoma incidence in the Swiss HIV cohort Study before and after highly active antiretroviral therapy. *Br J Cancer* 2008;99:800–4.
16. Polesel J, Clifford GM, Rickenbach M, et al. Non-Hodgkin lymphoma incidence in the Swiss HIV cohort Study before and after highly active antiretroviral therapy. *AIDS* 2008;22:301–6.
17. Clifford GM, Polesel J, Rickenbach M, et al. Swiss HIV Cohort. Cancer risk in the Swiss HIV cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst* 2005;97:425–32.
18. Shiels MS, Engels EA. Evolving epidemiology of HIV-associated malignancies. *Curr Opin HIV AIDS* 2017;12:6–11.
19. Guiguet M, Boué F, Cadranel J, et al. Clinical epidemiology group of the FHDH-ANRS CO4 cohort. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol* 2009;10: 1152–9.
20. Dubrow R, Qin L, Lin H, et al. Association of CD4+ T-cell count, HIV-1 RNA viral load, and antiretroviral therapy with Kaposi sarcoma risk among HIV-infected persons in the United States and Canada. *J Acquir Immune Defic Syndr* 2017;75:382–90.
21. Guech-Ongey M, Simard EP, Anderson WF, et al. AIDS-related Burkitt lymphoma in the United States: what do age and CD4 lymphocyte patterns tell us about etiology and/or biology? *Blood* 2010;116:5600–4.
22. Sabattini E, Bacci F, Sagramoso C. WHO classification of tumours of haematopoietic and lymphoid tissues in 2008: an overview. *Pathologica* 2010;102:83–7.
23. Gibson TM, Morton LM, Shiels MS, et al. Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study. *AIDS* 2014;28:2313–8.
24. Howlader N, Shiels MS, Mariotto AB, et al. Contributions of HIV to non-Hodgkin lymphoma mortality trends in the United States. *Cancer Epidemiol Biomarkers Prev* 2016;25: 1289–96.
25. Hishima T, Oyaizu N, Fujii T, et al. Decrease in Epstein–Barr virus-positive AIDS-related lymphoma in the era of highly active antiretroviral therapy. *Microbes Infect* 2006;8:1301–7.
26. Gopal S, Patel MR, Yanik EL, et al. Temporal trends in presentation and survival for HIV-associated lymphoma in the antiretroviral therapy era. *J Natl Cancer Inst* 2013;105:1221–9.
27. Shiels MS, Islam JY, Rosenberg PS, et al. Projected Cancer incidence rates and burden of incident Cancer cases in HIV-infected adults in the United States through 2030. *Ann Intern Med* 2018;168:866–73.
28. Nicolè S, Mengoli C, Marini G, et al. Characteristics of AIDS-related and non-AIDS-related cancers in an Italian cohort of HIV patients in the period 1996–2018. *J Int AIDS Soc* 2018;21 (S8):124.
29. Cobucci RNO, Lima PH, de Souza PC, et al. Cornetta M da C de M, Fernandes JV, Gonçalves AK. Assessing the impact of HAART on the incidence of defining and non-defining AIDS cancers among patients with HIV/AIDS: a systematic review. *J Infect Public Health* 2015; 8:1–10.
30. Schmidt C. The Cancer-HIV/AIDS treatment conundrum. *JNCI J Natl Cancer Inst* 2010;102: 1615–7.
31. Silverberg MJ, Chao C, Leyden WA, et al. HIV infection, immunodeficiency, viral replication, and the risk of Cancer. *Cancer Epidemiol Biomarkers Prev* 2011;20:2551–9.
32. Baker JV, Peng G, Rapkin J, et al. Terry Beirn community programs for clinical research on AIDS (CPCRA). CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS* 2008;22:841–8.
33. Monforte A, Abrams D, Pradier C, et al. Data collection on adverse events of anti-HIV drugs (D:a:D) Study group. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS* 2008;22: 2143–53.
34. Kesselring A, Gras L, Smit C, et al. Immunodeficiency as a risk factor for non-AIDS-defining malignancies in HIV-1-infected patients receiving combination antiretroviral therapy. *Clin Infect Dis* 2011;52:1458–65.
35. Bedimo RJ, McGinnis KA, Dunlap M, et al. Incidence of non-AIDS-defining malignancies in HIV-infected versus noninfected patients in the HAART era: impact of immunosuppression. *J Acquir Immune Defic Syndr* 2009;52:203–8.
36. Engels EA, Brock MV, Chen J, et al. Elevated incidence of lung Cancer among HIV-infected individuals. *J Clin Oncol* 2006;24:1383–8.
37. Shiels MS, Cole SR, Mehta SH, et al. Lung Cancer incidence and mortality among HIV-infected and HIV-uninfected injection drug users. *JAIDS J Acquir Immune Defic Syndr* 2010;55:510–5.
38. Reid E, Suneja G, Ambinder RF, et al. Cancer in people living with HIV, version 1.2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw* 2018;16:986–1017.
39. Coghill AE, Engels EA, Schymura MJ, et al. Risk of breast, prostate, and colorectal Cancer diagnoses among HIV-infected individuals in the United States. *J Natl Cancer Inst* 2018;110: 959–66.
40. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. *Ann Intern Med* 2008; 148:728–36.
41. Dauby N, De Wit S, Delforge M, et al. Characteristics of non-AIDS-defining malignancies in the HAART era: a clinico-epidemiological study. *J Int AIDS Soc* 2011;14:16.
42. Marcus JL, Chao CR, Leyden WA, et al. Prostate Cancer incidence and prostate-specific antigen testing among HIV-positive and HIV-negative men. *JAIDS J Acquir Immune Defic Syndr* 2014; 66:495–502.
43. Stone TW, McPherson M, Gail Darlington L. Obesity and Cancer: existing and new hypotheses for a causal connection. *EBioMedicine* 2018; 30:14–28.
44. Trushin SA, Algeciras-Schimnich A, Vlahakis SR, et al. Glycoprotein 120 binding to CXCR4 causes p38-dependent primary T cell death that is facilitated by, but does not require cell-associated CD4. *J Immunol* 2007;178:4846–53.
45. Anand AR, Ganju RK. HIV-1 gp120-mediated apoptosis of T cells is regulated by the membrane tyrosine phosphatase CD45. *J Biol Chem* 2006;281:12289–99.
46. Cummins NW, Badley AD. Mechanisms of HIV-associated lymphocyte apoptosis: 2010. *Cell Death Dis* 2010;1:e99.
47. Liu Z, Qiao L, Zhang Y, et al. ASPP2 plays a dual role in gp120-induced autophagy and apoptosis of neuroblastoma cells. *Front Neurosci* 2017;11:150.
48. Endo M, Inatsu A, Hashimoto K, et al. Human immunodeficiency virus-induced apoptosis of human breast cancer cells via CXCR4 is mediated by the viral envelope protein but does not require CD4. *Curr HIV Res* 2008;6:34–42.
49. Bumpers HL, Huang M-B, Powell M, et al. Effects of HIV-1 Nef, a cytotoxic viral protein, on the growth of primary colorectal cancer. *Cancer Biol Ther* 2005;4:72–6.
50. Harrington W, Bond V, Huang MB, et al. HIV Nef-M1 effects on colorectal Cancer growth in tumor-induced spleens and hepatic metastasis. *Mol Cell Pharmacol* 2009;1:85–91.
51. Singh S, Bond VC, Powell M, et al. CXCR4-gp120-IIIB interactions induce caspase-mediated apoptosis of prostate cancer cells and inhibit tumor growth. *Mol Cancer Ther* 2009;8: 178–84.
52. Marcus JL, Chao C, Leyden WA, et al. Survival among HIV-infected and HIV-uninfected individuals with common non-AIDS-defining cancers. *Cancer Epidemiol Biomarkers Prev* 2015;24:1167–73.
53. Coghill AE, Pfeiffer RM, Shiels MS, et al. Excess mortality among HIV-infected individuals with Cancer in the United States. *Cancer Epidemiol Biomarkers Prev* 2017;26:1027–33.
54. Zucchetto A, Virdone S, Taborelli M, et al. Non-AIDS-defining Cancer mortality. *JAIDS J Acquir Immune Defic Syndr* 2016;73:190–6.
55. Suneja G, Shiels MS, Angulo R, et al. Cancer treatment disparities in HIV-infected individuals in the United States. *J Clin Oncol* 2014;32:2344–50.
56. Hleyhel M, Belot A, Bouvier A-M, et al. Trends in survival after cancer diagnosis among HIV-infected individuals between 1992 and 2009. Results from the FHDH-ANRSCO4 cohort. *Int J Cancer* 2015;137:2443–53.

57. Cingolani A, Cozzi Lepri A, Teofili L, et al. Survival and predictors of death in people with HIV-associated lymphoma compared to those with a diagnosis of lymphoma in general population. *PLoS One* 2017;12:e0186549.
58. Dryden-Peterson S, Bvochora-Nsingo M, Suneja G, et al. HIV infection and survival among women with cervical cancer. *J Clin Oncol* 2016;34:3749–57.
59. Leitch H, Trudeau M, Routy J-P. Effect of protease inhibitor-based highly active antiretroviral therapy on survival in HIV-associated advanced Kaposi's sarcoma patients treated with chemotherapy. *HIV Clin Trials* 2003;4:107–14.
60. Hoffmann C, Tabrizian S, Wolf E, et al. Survival of AIDS patients with primary central nervous system lymphoma is dramatically improved by HAART-induced immune recovery. *AIDS* 2001; 15:2119–27.
61. Castillo JJ, Echenique IA. Rituximab in combination with chemotherapy versus chemotherapy alone in HIV-associated non-Hodgkin lymphoma: a pooled analysis of 15 prospective studies. *Am J Hematol* 2012;87:330–3.
62. Uldrick TS, Pipkin S, Scheer S, et al. Risk factors for death and temporal trends in overall survival in patients with AIDS-associated primary central nervous system lymphoma (AIDS-PCNSL). *Infect Agent Cancer* 2012;7(S1):O18.
63. Vaccher E, Spina M, di Gennaro G, et al. Concomitant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy plus highly active antiretroviral therapy in patients with human immunodeficiency virus-related, non-Hodgkin lymphoma. *Cancer* 2001;91:155–63.
64. Martinez V, Caumes E, Gambotti L, et al. Remission from Kaposi's sarcoma on HAART is associated with suppression of HIV replication and is independent of protease inhibitor therapy. *Br J Cancer* 2006;94:1000–6.
65. Wong AYJ, Marcotte S, Laroche M, et al. Safety and efficacy of CHOP for treatment of diffuse large B-cell lymphoma with different combination antiretroviral therapy regimens: SCULPT study. *Antivir Ther* 2013;18:699–707.
66. Ibrahim K, Milliken S. Protease Inhibitor vs. non-protease inhibitor based antiretroviral therapy in HIV-infected patients with Hodgkin and non-Hodgkin lymphoma receiving chemotherapy. *Blood* 2013;122:3843.
67. Cattelan AM, Calabrò ML, Gasperini P, et al. Acquired immunodeficiency syndrome-related Kaposi's sarcoma regression after highly active antiretroviral therapy: biologic correlates of clinical outcome. *J Natl Cancer Inst Monogr* 2001; (28): 44–49
68. Pinto-Almeida T, Torres T, Rosmaninho A, et al. Letter: Penile Kaposi sarcoma: a case of complete resolution with highly active antiretroviral therapy alone. *Dermatol Online J* 2011;17:12.
69. Kumarasamy N, Venkatesh KK, Devaleenol B, et al. Regression of Kaposi's sarcoma lesions following highly active antiretroviral therapy in an HIV-infected patient. *Int J STD AIDS* 2008;19: 786–8.
70. Leder HA, Galor A, Peters GB, et al. Resolution of conjunctival Kaposi sarcoma after institution of highly active antiretroviral therapy alone. *Br J Ophthalmol* 2008;92:151.
71. Hallit RR, Afridi M, Sison R, et al. AIDS-related lymphoma: resolution with antiretroviral therapy alone. *J Int Assoc Provid AIDS Care* 2014;13: 313–5.
72. Lim DH, Rhee J-Y, Park KW. Stage IV advanced diffuse large B-cell lymphoma in human immunodeficiency virus infection with achieving cure by using highly active antiretroviral therapy alone: a case report. *Int J STD AIDS* 2017;28:932–6.
73. Travi G, Ferreri AJM, Cinque P, et al. Long-term remission of HIV-associated primary CNS lymphoma achieved with highly active antiretroviral therapy alone. *J Clin Oncol* 2012;30:e119–21.
74. Katsidzira L, Ramsay A, Makunike-Mutasa R, et al. Complete regression of early diffuse B-cell lymphoma in an HIV-positive patient on antiretroviral therapy alone. *Int J STD AIDS* 2011;22: 409–10.
75. Heard I, Schmitz V, Costagliola D, et al. Early regression of cervical lesions in HIV-seropositive women receiving highly active antiretroviral therapy. *AIDS* 1998;12:1459–64.
76. Blitz S, Baxter J, Raboud J, et al. Canadian Women's HIV Study group. Evaluation of HIV and highly active antiretroviral therapy on the natural history of human papillomavirus infection and cervical cytopathologic findings in HIV-positive and high-risk HIV-negative women. 2013;208.
77. Mosam A, Shaik F, Uldrick TS, et al. A randomized controlled trial of highly active antiretroviral therapy versus highly active antiretroviral therapy and chemotherapy in therapy-naive patients with HIV-associated Kaposi sarcoma in South Africa. *JAIDS J Acquir Immune Defic Syndr* 2012;60:150–7.
78. Sombogaard F, Franssen EJF, Terpstra WE, et al. Outcome effects of antiretroviral drug combinations in HIV-positive patients with chemotherapy for lymphoma: a retrospective analysis. *Int J Clin Pharmacol* 2018;40:1402–8.
79. Lim ST, Karim R, Nathwani BN, et al. AIDS-related Burkitt's lymphoma versus diffuse large-cell lymphoma in the pre-highly active antiretroviral therapy (HAART) and HAART eras: significant differences in survival with standard chemotherapy. *J Clin Oncol* 2005;23:4430–8.
80. Simcock M, Blasko M, Karrer U, et al. Swiss HIV cohort Study. Treatment and prognosis of AIDS-related lymphoma in the era of highly active antiretroviral therapy: findings from the Swiss HIV cohort Study. *Antivir Ther* 2007;12:931–9.
81. Olszewski AJ, Castillo JJ. Outcomes of HIV-associated Hodgkin lymphoma in the era of antiretroviral therapy. *AIDS* 2016;30:787–96.
82. Chiao EY, Giordano TP, Richardson P, et al. Human immunodeficiency virus-associated squamous cell cancer of the anus: epidemiology and outcomes in the highly active antiretroviral therapy era. *J Clin Oncol* 2008;26:474–9.
83. Kato T, Ieki R, Saito E, et al. A long-term survival case of small cell lung cancer in an HIV-infected patient. *Jpn J Clin Oncol* 2005;35: 349–52.
84. Modest GA, Cooley TP, Zacks JF. HIV and refractory anemia with excess blasts (RAEB). *Am J Hematol* 2002;70:318–9.
85. Leng LK, Pancharoen C, Bunupuradah T, et al. Regression of a cervical spinal mass following highly active antiretroviral therapy (HAART) in child with advanced human immunodeficiency virus (HIV) disease. *J Med Assoc Thai* 2007;90: 1937–42.
86. Vilchez RA, Finch CJ, Jorgensen JL, et al. The clinical epidemiology of Hodgkin lymphoma in HIV-infected patients in the highly active antiretroviral therapy (HAART) era. *Medicine (Baltimore)* 2003;82:77–81.
87. Lavolé A, Chouaïd C, Baudrin L, et al. Effect of highly active antiretroviral therapy on survival of HIV infected patients with non-small-cell lung cancer. *Lung Cancer* 2009;65:345–50.
88. Rudek MA, Moore PC, Mitsuyasu RT, et al. A phase 1/pharmacokinetic study of sunitinib in combination with highly active antiretroviral therapy in human immunodeficiency virus-positive patients with cancer: AIDS malignancy consortium trial AMC 061. *Cancer* 2014;120:1194–202.
89. Berretta M, Caraglia M, Martellotta F, et al. Drug-drug interactions based on pharmacogenetic profile between highly active antiretroviral therapy and Antiblastic chemotherapy in Cancer patients with HIV infection. *Front Pharmacol* 2016;7:71.
90. Torres HA, Rallapalli V, Saxena A, et al. Efficacy and safety of antiretrovirals in HIV-infected patients with cancer. *Clin Microbiol Infect* 2014;20:O672–9.
91. Mounier N, Katlama C, Costagliola D, et al. Drug interactions between antineoplastic and antiretroviral therapies: implications and management for clinical practice. *Crit Rev Oncol Hematol* 2009;72:10–20.
92. Deeken JF, Pantanowitz L, Dezube BJ. Targeted therapies to treat non-AIDS-defining cancers in patients with HIV on HAART therapy: treatment considerations and research outlook. *Curr Opin Oncol* 2009;21:445–54.
93. Di Francia R, Fierro C, Di Paolo M. Selected pharmacogenetic panel test for toxicity prevention of drug-drug interactions between highly active antiretroviral therapy (HAART) and antiblastic. *World Cancer Res J* 2015;2:e492.
94. Department of Health and Human Services. Panel on antiretroviral guidelines for adults and adolescents. *Guidelines for the use of antiretroviral agents in adults and adolescents with HIV*. Washington, DC: Department of Health and Human Services, 2019.
95. Crum-Cianflone NF, Hullsiek KH, Marconi V, et al. The impact of nelfinavir exposure on cancer development among a large cohort of HIV-infected patients. *J Acquir Immune Defic Syndr* 2009;51:305–9.
96. Boettiger DC, Sabin CA, Grulich A, et al. Data collection on adverse events of anti-HIV drugs (D:a:D) study group. Is nelfinavir exposure associated with cancer incidence in HIV-positive individuals? *AIDS* 2016;30:1629–37.
97. Bruyand M, Ryom L, Shepherd L, et al. Cancer risk and use of Protease Inhibitor or non-nucleoside reverse transcriptase Inhibitor–based combination antiretroviral therapy. *JAIDS J Acquir Immune Defic Syndr* 2015;68: 568–77.
98. Bohlius J, Valeri F, Maskew M, et al. Kaposi's sarcoma in HIV-infected patients in South Africa: multicohort study in the antiretroviral therapy era. *Int J Cancer* 2014;135:2644–52.
99. Mocroft A, Kirk O, Clumeck N, et al. The changing pattern of Kaposi sarcoma in patients with HIV, 1994-2003. *Cancer* 2004;100:2644–54.
100. Chao C, Leyden WA, Xu L, et al. Exposure to antiretroviral therapy and risk of cancer in HIV-infected persons. *AIDS* 2012;26:2223–31.

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101. Lodi S, Guiguet M, Costagliola D, et al. CASCADE collaboration the C. Kaposi sarcoma incidence and survival among HIV-infected homosexual men after HIV seroconversion. *J Natl Cancer Inst* 2010;102:784–92.
102. Burgi A, Brodine S, Wegner S, et al. Incidence and risk factors for the occurrence of non-AIDS-defining cancers among human immunodeficiency virus-infected individuals. *Cancer* 2005; 104:1505–11.
103. Clifford GM, Rickenbach M, Lise M, et al. Hodgkin lymphoma in the Swiss HIV cohort Study. *Blood* 2009;113:5737–42.
104. Bohlius J, Schmidlin K, Boué F, et al. Collaboration of Observational HIV Epidemiological Research Europe. HIV-1-related Hodgkin lymphoma in the era of combination antiretroviral therapy: incidence and evolution of $CD4^+$ T-cell lymphocytes. *Blood* 2011;117:6100–8.
105. Lanoy E, Rosenberg PS, Fily F, et al. HIV-associated Hodgkin lymphoma during the first months on combination antiretroviral therapy. *Blood* 2011;118:44–9.
106. Cheng Z, Shan F, Liu J, et al. Clinical and computed tomography findings in Chinese lung cancer patients with HIV infection: a multi-center study. *Thorac cancer* 2017;8:238–45.
107. Bruyand M, Le Marec F, Lavole A, et al. Protease inhibitors exposure is not related to lung cancer risk in HIV smoker patients: a nested case-control study. *AIDS* 2015;29:1105–9.
108. Kirk GD, Merlo C, O'Driscoll P, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis* 2007;45:103–10.
109. van der Snoek EM, van der Ende ME, den Hollander JC, et al. Use of highly active antiretroviral therapy is associated with lower prevalence of anal intraepithelial neoplastic lesions and lower prevalence of human papillomavirus in HIV-infected men who have sex with men. *Sex Transm Dis* 2012;39:495–500.
110. Duncan KC, Chan KJ, Chiu CG, et al. HAART slows progression to anal cancer in HIV-infected MSM. *AIDS* 2015;29:305–11.
111. Crum-Cianflone NF, Hullsiek KH, Marconi VC, et al. Infectious disease clinical research program HIV working group. Anal cancers among HIV-infected persons: HAART is not slowing rising incidence. *AIDS* 2010;24:535–43.
112. Pappou EP, Magruder JT, Fu T, et al. Prognostic and predictive clinicopathologic factors of squamous Anal Canal Cancer in HIV-positive and HIV-negative patients: does HAART influence outcomes? *World J Surg* 2018;42:876–83.
113. Sahasrabuddhe VV, Shiels MS, McGlynn KA, et al. The risk of hepatocellular carcinoma among individuals with acquired immunodeficiency syndrome in the United States. *Cancer* 2012;118:6226–33.
114. Olivero OA. Mechanisms of genotoxicity of nucleoside reverse transcriptase inhibitors. *Environ Mol Mutagen* 2007;48:215–23.
115. Benhammou V, Warszawski J, Bellec S, et al. Incidence of cancer in children perinatally exposed to nucleoside reverse transcriptase inhibitors. *AIDS* 2008;22:2165–77.
116. Brogly S, Williams P, Seage GR, et al. In utero nucleoside reverse transcriptase inhibitor exposure and cancer in HIV-uninfected children: an update from the pediatric AIDS clinical trials group 219 and 219C cohorts. *J Acquir Immune Defic Syndr* 2006;41:535–6.
117. Hleyhel M, Goujon S, Delteil C, et al. ANRS French perinatal cohort Study group. Risk of cancer in children exposed to didanosine in utero. *AIDS* 2016;30:1245–56.
118. Hleyhel M, Goujon S, Sibiude J, et al. Risk of cancer in children exposed to antiretroviral nucleoside analogues *in utero*: the French experience. *Environ Mol Mutagen* 2017;60:404–9.
119. Portsmouth S, Stebbing J, Gill J, et al. A comparison of regimens based on non-nucleoside reverse transcriptase inhibitors or protease inhibitors in preventing Kaposi's sarcoma. *AIDS* 2003; 17:F17–22.
120. Stebbing J, Portsmouth S, Nelson M, et al. The efficacy of ritonavir in the prevention of AIDS-related Kaposi's sarcoma. *Int J Cancer* 2004;108:631–3.
121. Gantt S, Cattamanchi A, Krantz E, et al. Reduced human herpesvirus-8 oropharyngeal shedding associated with protease inhibitor-based antiretroviral therapy. *J Clin Virol* 2014;60:127–32.
122. Gill J, Bourboulia D, Wilkinson J, et al. Prospective study of the effects of antiretroviral therapy on Kaposi sarcoma-associated herpesvirus infection in patients with and without Kaposi sarcoma. *J Acquir Immune Defic Syndr* 2002;31: 384–90.
123. Bani-Sadr F, Fournier S, Molina JM. Relapse of Kaposi's sarcoma in HIV-infected patients switching from a protease inhibitor to a non-nucleoside reverse transcriptase inhibitor-based highly active antiretroviral therapy regimen. *AIDS* 2003;17:1580–1.
124. Paparizos VA, Kyriakis KP, Kourkounti S, et al. The influence of a HAART regimen on the expression of HIV-associated Kaposi sarcoma. *J Acquir Immune Defic Syndr* 2008;49:111.
125. Ridolfo AL, Corbellino M, Tosca N, et al. Is switching protease inhibitor-based effective antiretroviral therapy safe in patients with AIDS-associated Kaposi's sarcoma? *AIDS* 2004;18: 1224–6.
126. Philibert P, Chiche L, Caillères S, et al. HHV8 and Kaposi's sarcoma: should we really give up protease inhibitors in all HIV-infected patients? *AIDS* 2017;31:2167–9.
127. Simonetti FR, Ricaboni D, Cattaneo D, et al. Relapse of Kaposi's sarcoma and HHV-8 viremia in an HIV-infected patient switching from protease inhibitor to integrase inhibitor-based antiretroviral therapy. *J Clin Virol* 2016;74:75–7.
128. Cozzi-Lepri A, Zangerle R, Machala L, et al. Incidence of cancer and overall risk of mortality in individuals treated with raltegravir-based and non-raltegravir-based combination antiretroviral therapy regimens. *HIV Med* 2018;19:102–17.
129. Gulick RM, Su Z, Flexner C, et al. Phase 2 Study of the safety and efficacy of Vicriviroc, a CCR5 Inhibitor, in HIV-1–infected, treatment-experienced patients: AIDS Clinical Trials Group 5211. *J Infect Dis* 2007;196:304–12.
130. Caseiro MM, Nelson M, Diaz RS, et al. Vicriviroc plus optimized background therapy for treatment-experienced subjects with CCR5 HIV-1 infection: final results of two randomized phase III trials. *J Infect* 2012;65:326–35.
131. Gulick RM, Fatkenheuer G, Burnside R, et al. Five-year safety evaluation of maraviroc in HIV-1-infected treatment-experienced patients. *J Acquir Immune Defic Syndr* 2014;65:78–81.
132. Krishnan S, Schouten JT, Jacobson DL, et al. Incidence of non-AIDS-defining cancer in antiretroviral treatment-naïve subjects after antiretroviral treatment initiation: an ACTG longitudinal linked randomized trials analysis. *Oncology* 2011;80:42–9.
133. Mbang PA, Kowalkowski MA, Amirian ES, et al. Association between time on Protease inhibitors and the incidence of squamous cell carcinoma of the anus among U.S. male veterans. *PLoS One* 2015;10:e0142966.
134. Lusivika-Nzinga C, Selinger-Leneman H, Grabar S, et al. Performance of the marginal structural cox model for estimating individual and joined effects of treatments given in combination. *BMC Med Res Methodol* 2017;17:160.
135. Grabar S, Selinger-Leneman H, Abramowitz L, et al. Anal cancer risk and use of a protease inhibitor: a nested case-control study within the ANRS CO4-FHDH cohort. *J Int AIDS Soc* 2018; 21(S8):121–2.
136. Gills JJ, LoPiccolo J, Tsurutani J, et al. Nelfinavir, a Lead HIV Protease Inhibitor, is a broad-Spectrum, anticancer agent that induces endoplasmic reticulum stress, autophagy, and apoptosis in vitro and in vivo. *Clin Cancer Res* 2007;13:5183–94.
137. Srirangam A, Mitra R, Wang M, et al. Effects of HIV protease inhibitor ritonavir on Akt-regulated cell proliferation in breast cancer. *Clin Cancer Res* 2006;12:1883–96.
138. Shim JS, Rao R, Beebe K, et al. Selective inhibition of HER2-positive breast Cancer cells by the HIV Protease Inhibitor nelfinavir. *JNCI J Natl Cancer Inst* 2012;104:1576–90.
139. Soprano M, Sorriento D, Rusciano MR, et al. Oxidative stress mediates the antiproliferative effects of nelfinavir in breast cancer cells. *PLoS One* 2016;11:e0155970.
140. Koltai T. Nelfinavir and other protease inhibitors in cancer: mechanisms involved in anticancer activity. *F1000Research* 2015;4:9.
141. Maksimovic-Ivanic D, Fagone P, McCubrey J, et al. HIV-protease inhibitors for the treatment of cancer: repositioning HIV protease inhibitors while developing more potent NO-hybridized derivatives? *Int J Cancer* 2017;140:1713–26.
142. Bernstein WB, Dennis PA. Repositioning HIV protease inhibitors as cancer therapeutics. *Curr Opin HIV AIDS* 2008;3:666–75.
143. Goda J, Pachpor T, Basu T, et al. Targeting the AKT pathway: repositioning HIV protease inhibitors as radiosensitizers. *Indian J Med Res* 2016; 143:145–59.
144. Faes S, Dormond O. PI3K and AKT: unfaithful Partners in Cancer. *Int J Mol Sci* 2015;16: 21138–52.
145. Radisavljevic Z. AKT as locus of cancer phenotype. *J Cell Biochem* 2015;116:1–5.
146. Martini M, De Santis MC, Braccini L, et al. PI3K/AKT signaling pathway and cancer: an updated review. *Ann Med* 2014;46:372–83.
147. Polivka J, Janku F. Molecular targets for cancer therapy in the PI3K/AKT/mTOR pathway. *Pharmacol Ther* 2014;142:164–75.
148. Zheng H-C. The molecular mechanisms of chemoresistance in cancers. *Oncotarget* 2017;8: 59950–64.
149. Farrand L, Oh S-W, Song YS, et al. Phytochemicals: a multitargeted approach to gynecologic cancer therapy. *Biomed Res Int* 2014;2014: 890141.

150. Miyata Y, Nakamoto H, Neckers L. The therapeutic target Hsp90 and cancer hallmarks. *Curr Pharm Des* 2013;19:347–65.
151. Kim JG, Lee SC, Kim O-H, et al. HSP90 inhibitor 17-DMAG exerts anticancer effects against gastric cancer cells principally by altering oxidant-antioxidant balance. *Oncotarget* 2017;8: 56473–89.
152. Manalo RVM, Medina PMB. The endoplasmic reticulum stress response in disease pathogenesis and pathophysiology. *Egypt J Med Hum Genet* 2018;19:59–68.
153. Arodola O, Soliman M. Could the FDA-approved anti-HIV PR inhibitors be promising anticancer agents? An answer from enhanced docking approach and molecular dynamics analyses. *Drug Des Dev Ther* 2015;9:6055.
154. Lutz WK. The Viracept (nelfinavir)–ethyl methanesulfonate case: a threshold risk assessment for human exposure to a genotoxic drug contamination? *Toxicol Lett* 2009;190:239–42.
155. Gantt S, Carlsson J, Ikoma M, et al. The HIV Protease Inhibitor nelfinavir inhibits Kaposi's sarcoma-associated herpesvirus replication in vitro. *Antimicrob Agents Chemother* 2011;55: 2696–703.
156. Brown JA, Pack LR, Fowler JD, et al. Pre-steady-state kinetic analysis of the incorporation of anti-HIV nucleotide analogs catalyzed by human X- and Y-family DNA polymerases. *Antimicrob Agents Chemother* 2011;55:276–83.
157. Perna A, Lucariello A, Sellitto C, et al. Different cell cycle modulation in SKOV-3 ovarian Cancer cell line by anti-HIV drugs. *Oncol Res Featur Preclin Clin Cancer Ther* 2017;25:1617–24.
158. Carlini F, Ridolfi B, Molinari A, et al. The reverse transcription inhibitor abacavir shows anticancer activity in prostate cancer cell lines. 2010;5:e14221.
159. Landriscina M, Spadafora C, Cignarelli M, et al. Anti-tumor activity of non-nucleosidic reverse transcriptase inhibitors. *Curr Pharm Des* 2007; 13:737–47.
160. Brüning A, Burger P, Gingelmaier A, et al. The HIV reverse transcriptase inhibitor tenofovir induces cell cycle arrest in human cancer cells. *Invest New Drugs* 2012;30:1389–95.
161. Crespan E, Garbelli A, Amoroso A, et al. Exploiting the nucleotide substrate specificity of repair DNA polymerases to develop novel anticancer agents. *Molecules* 2011;16:7994–8019.
162. Young MJ. Off-target effects of drugs that disrupt human mitochondrial DNA maintenance. *Front Mol Biosci* 2017;4:74.
163. Xiao-Jie L, Hui-Ying X, Qi X, et al. LINE-1 in cancer: multifaceted functions and potential clinical implications. *Genet Med* 2016;18:431–9.
164. Mangiacasale R, Pittoggi C, Sciamanna I, et al. Exposure of normal and transformed cells to nevirapine, a reverse transcriptase inhibitor, reduces cell growth and promotes differentiation. *Oncogene* 2003;22:2750–61.
165. Hecht M, Harrer T, Korber V, et al. Cytotoxic effect of Efavirenz in BxPC-3 pancreatic cancer cells is based on oxidative stress and is synergistic with ionizing radiation. *Oncol Lett* 2017;15: 1728–36.
166. Landriscina M, Bagalà C, Piscazzi A, et al. Nevirapine restores androgen signaling in hormone-refractory human prostate carcinoma cells both in vitro and in vivo. *Prostate* 2009;69:744–54.
167. Hecht M, Erber S, Harrer T, et al. Efavirenz has the highest anti-proliferative effect of non-nucleoside reverse transcriptase inhibitors against pancreatic cancer cells. *PLoS One* 2015; 10:e0130277.
168. Brüning A, Jückstock J, Kost B, et al. Induction of DNA damage and apoptosis in human leukemia cells by efavirenz. *Oncol Rep* 2017;37:617–21.
169. Sciamanna I, Landriscina M, Pittoggi C, et al. Inhibition of endogenous reverse transcriptase antagonizes human tumor growth. *Oncogene* 2005;24:3923–31.
170. Ulrike K, Markus H, Thomas H, et al. NNRTI-based antiretroviral therapy may increase risk of radiation induced side effects in HIV-1-infected patients. *Radiother Oncol* 2015;116:323–30.
171. Varadarajan J, McWilliams MJ, Hughes SH. Treatment with suboptimal doses of raltegravir leads to aberrant HIV-1 integrations. *Proc Natl Acad Sci USA* 2013;110:14747–52.
172. Varadarajan J, McWilliams MJ, Mott BT, et al. Drug resistant integrase mutants cause aberrant HIV integrations. *Retrovirology* 2016;13:71.
173. Williamson EA, Damiani L, Leitao A, et al. Targeting the transposase domain of the DNA repair component Metnase to enhance chemotherapy. *Cancer Res* 2012;72:6200–8.
174. Pervaiz A, Zepp M, Mahmood S, et al. CCR5 blockage by maraviroc: a potential therapeutic option for metastatic breast cancer. *Cell Oncol* 2018;42:93–106.
175. Casagrande N, Borghese C, Visser L, et al. CCR5 antagonism by maraviroc inhibits Hodgkin lymphoma microenvironment interactions and xenograft growth. *Haematologica* 2018;104: 564–75.
176. Velasco-Velazquez M, Jiao X, De La Fuente M, et al. CCR5 antagonist blocks metastasis of basal breast Cancer cells. *Cancer Res* 2012;72:3839–50.
177. Tanabe Y, Sasaki S, Mukaida N, et al. Blockade of the chemokine receptor, CCR5, reduces the growth of orthotopically injected colon cancer cells via limiting cancer-associated fibroblast accumulation. *Oncotarget* 2016;7:48335–45.
178. Sicoli D, Jiao X, Ju X, et al. CCR5 receptor antagonists block metastasis to bone of v-Src oncogene-transformed metastatic prostate cancer cell lines. *Cancer Res* 2014;74:7103–14.
179. Halama N, Zoernig I, Berthel A, et al. Tumoral immune cell exploitation in colorectal cancer metastases can be targeted effectively by anti-CCR5 therapy in Cancer patients. *Cancer Cell* 2016;29:587–601.
180. Monini P, Sgadari C, Grosso MG, et al. Clinical course of classic Kaposi's sarcoma in HIV-negative patients treated with the HIV protease inhibitor indinavir. *AIDS* 2009;23:534–8.
181. Brunner TB, Geiger M, Grabenbauer GG, et al. Phase I trial of the human immunodeficiency virus protease inhibitor nelfinavir and chemoradiation for locally advanced pancreatic cancer. *J Clin Oncol* 2008;26:2699–706.
182. Rengan R, Mick R, Pryma D, et al. A phase I trial of the HIV protease inhibitor nelfinavir with concurrent chemoradiotherapy for unresectable stage IIIA/IIIB non-small cell lung cancer: a report of toxicities and clinical response. *J Thorac Oncol* 2012;7:709–15.
183. Buijsen J, Lammering G, Jansen RLH, et al. Phase I trial of the combination of the Akt inhibitor nelfinavir and chemoradiation for locally advanced rectal cancer. *Radiother Oncol* 2013; 107:184–8.
184. Driessen C, Muller R, Novak U, et al. The HIV protease inhibitor nelfinavir in combination with bortezomib and dexamethasone (NVd) has excellent activity in patients with advanced, proteasome inhibitor-refractory multiple myeloma: a multicenter phase II trial (SAKK 39/13). 58th Annual Meeting of the American Society of Hematology, ASH 2016. December 3–6, 2016; 128
185. Blumenthal GM, Gills JJ, Ballas MS, et al. A phase I trial of the HIV protease inhibitor nelfinavir in adults with solid tumors. *Oncotarget* 2014;5:8161–72.
186. Alonso-Basanta M, Fang P, Maity A, et al. A phase I study of nelfinavir concurrent with temozolomide and radiotherapy in patients with glioblastoma multiforme. *J Neurooncol* 2014;116:365–72.
187. Wilson JM, Fokas E, Dutton SJ, et al. ARCII: a phase II trial of the HIV protease inhibitor nelfinavir in combination with chemoradiation for locally advanced inoperable pancreatic cancer. *Radiother Oncol* 2016;119:306–11.
188. Hampson L, Maranga IO, Masinde MS, et al. A Single-arm, proof-of-concept trial of Lopimune (Lopinavir/ritonavir) as a treatment for HPV-related pre-invasive cervical disease. *PLoS One* 2016; 11: e0147917.
189. Modoni S, Landriscina M, Fabiano A, et al. Reinduction of cell differentiation and 131I uptake in a poorly differentiated thyroid tumor in response to the reverse transcriptase (RT) inhibitor nevirapine. *Cancer Biother Radiopharm* 2007;22:289–95.
190. Landriscina M, Modoni S, Fabiano A, et al. Cell differentiation and iodine-131 uptake in poorly differentiated thyroid tumour in response to nevirapine. *Lancet Oncol* 2006;7:877–9.
191. Hoover AC, Milhem MM, Anderson CM, et al. Efficacy of nelfinavir as monotherapy in refractory adenoid cystic carcinoma: results of a phase II clinical trial. *Head Neck* 2015;37:722–6.
192. Houede N, Pulido M, Mourey L, et al. A phase II trial evaluating the efficacy and safety of efavirenz in metastatic castration-resistant prostate cancer. *Oncologist* 2014;19:1227–8.
193. Ahluwalia MS, Patton C, Stevens G, et al. Phase II trial of ritonavir/lopinavir in patients with progressive or recurrent high-grade gliomas. *J Neurooncol* 2011;102:317–21.
194. Mani D, Neil N, Israel R, et al. A retrospective analysis of AIDS-associated Kaposi's sarcoma in patients with undetectable HIV viral loads and CD4 counts greater than 300 cells/mm^3. *J Int Assoc Physicians AIDS Care (Chic)* 2009;8:279–85.
195. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer* 2008;123:187–94.
196. van Leeuwen MT, Vajdic CM, Middleton MG, et al. Continuing declines in some but not all HIV-associated cancers in Australia after widespread use of antiretroviral therapy. *AIDS* 2009; 23:2183–90.
197. Wu Y, Yoder A. Chemokine coreceptor signaling in HIV-1 infection and pathogenesis. *PLoS Pathog* 2009;5:e1000520.
198. European AIDS Clinical Society. *EACS guidelines 9.1*. Brussels: European AIDS Clinical Society, 2018.

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