HIV patients' altered cancer burden: behaviour, immunodeficiency or drug-induced mutagenesis?

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ABSTRACT

Currently, 38 million people are living with HIV (PLWH) and this number is increasing by over a million per year. PLWH have a lower life expectancy than the healthy population. This is partially due to the higher cancer incidence in PLWH. Kaposi sarcoma, non-Hodgkin lymphoma and cervical cancer have the highest increased risk in the untreated PLWH population and are therefore termed the AIDS-defining cancer types (ADC). However, after the introduction of highly active antiretroviral therapy (HAART) in 1996, the incidence of ADCs has dramatically decreased. Unfortunately, this is not the case for non-AIDS-defining cancers (NADC), which have only increased in incidence in PLWH. This review describes the cancer incidences in PLWH, the change of these incidences after the introduction of HAART and gives an overview of the potential causes for the rise in NADCs. First, behavioural risk factors play a role in cancer development in PLWH, intravenous drug use, smoking, and alcohol abuse are all more common in PLWH. Co-infections with viruses related to cancer development (e.g. human papillomavirus and cervical cancer) are also more prevalent in PLWH. Moreover, some specific HAART drugs have been found to cause DNA damage, potentially leading to carcinogenesis. It is useful to further study drug-induced mutagenesis and include prescribed drug information and risk behaviour for PLWH in the cohort studies. This information can further improve HAART treatment, as HAART is an essential daily component for PLWH in improving quality of life and extending their lifespan.

ABBREVIATIONS

AIDS = Acquired immunodeficiency syndrome
HIV = Human immunodeficiency virus
PLWH = People living with HIV
RT = Reverse Transcriptase
FDA = Food and Drug Administration
AZT = Azidothymidine
NRTI = Nucleoside RT inhibitor
NNRTI = Non-NRTI
PI = Protease inhibitor
INSTI = Integrase strand transfer inhibitor
HAART = Highly active antiretroviral therapy
cART = Combined antiretroviral therapy
ADC = AIDS-defining cancer
NADC = Non-AIDS-defining cancer
VRNADC = Virus-related NADC
VUNADC = Virus-unrelated NADC
KS = Kaposi sarcoma
NHL = Non-Hodgkin lymphoma
ICC = Invasive cervical cancer
SIR = Standardized incidence ratio
IDU = Intravenous drug user
HL = Hodgkin lymphoma

1. INTRODUCTION

1.1 Historical perspective

1981 was the first detection of acquired immunodeficiency syndrome (AIDS).[1] Already within a year, it was the most common disease in gay men and intravenous drug users.[2] In addition, as there was no test to screen for AIDS in blood banks between 1981 and 1984, approximately 15 0000 haemophiliacs developed AIDS after transfusion of contaminated blood supply.[2] The main characteristic of AIDS patients was the low amount of CD4 T cells. A retrovirus, human immunodeficiency virus (HIV), was found to be targeting these cells and identified as the cause for AIDS development.[2,3] In the present day, the total number of people living with HIV (PLWH) was estimated to be nearly 38 million, of which 1.5 million were people infected with HIV in 2020.[4]

1.2 Infection mechanism

The HIV viral particles bind to, and subsequently infect, cells expressing the CD4 receptor (**Figure 1**).[2,5–7] These CD4 cells are predominantly T-cells. Upon cellular entry, the viral reverse transcriptase (RT) is recruited in the cytoplasm. The genetic information present in the viral particle is an RNA strand, therefore the RT is needed to synthesize a double-stranded DNA version of the viral RNA genome. The viral DNA enters the nucleus and is inserted into the host genome using HIV integrase. Integration of the viral DNA is not random; it prefers active regions of the host genome which enhances replication speed.[2,3] After integration, the transcription-translation machinery of the host is used to synthesize new viral particles, which assemble at the plasma membrane and

bud from the cell surface. HIV is able to induce programmed cell death in CD4 T cells, resulting in immunodeficiency.[5,8,9] Additionally, early upon HIV infection the immune system gets activated and cytokine release is initiated.[10] However, HIV destroys the lymphocytes needed to regulate cytokine secretion, subsequently causing chronic inflammation. The hijacking of the host immune system by HIV ultimately leads to the development of the disease AIDS. [8,9]

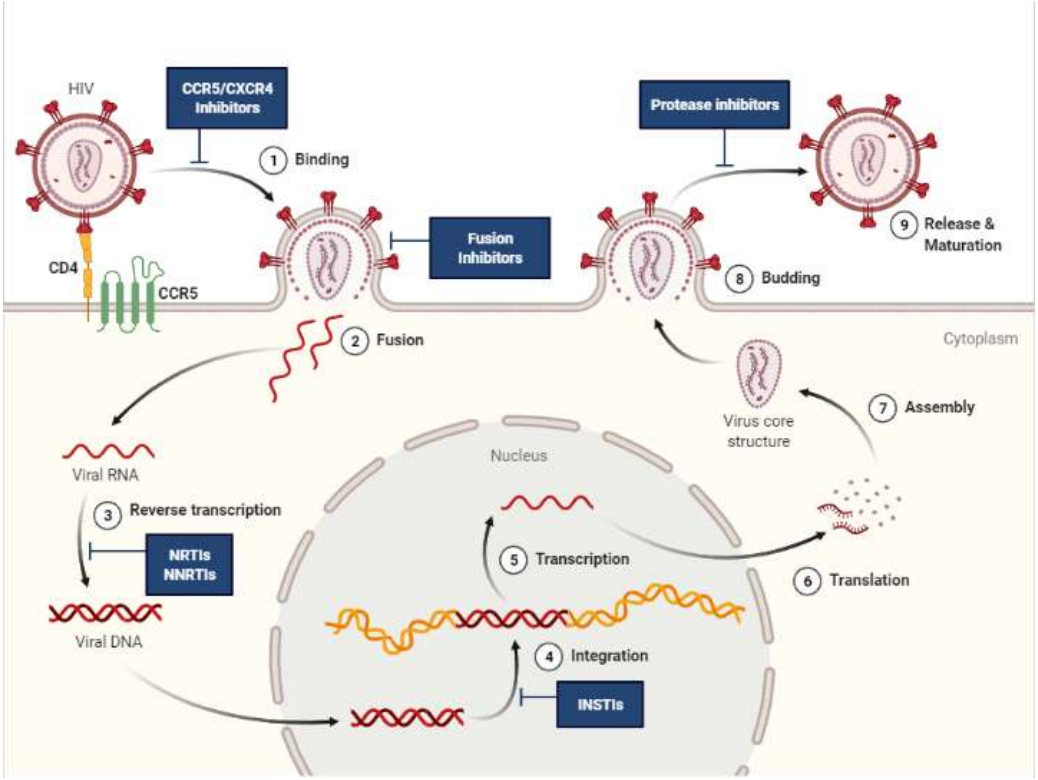

FIGURE 1. The HIV replication cycle and therapeutic target points for the antiviral drugs. *Reprinted from "HIV Sites for Therapeutic Intervention", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates*

1.3 Development and consequences of AIDS

Disease progression upon HIV infection can vary, but it often takes several years to develop symptoms.[11] PLWH are diagnosed with AIDS when levels of circulating CD4 T cells below drop below the threshold of 200 CD4 cells/µL.[12] Healthy HIV-negative people typically have 500-1000 CD4 cells/µL. Thus, in PLWH without an official AIDS diagnosis, a slight immunodeficiency remains. PLWH suffer from e.g. fatigue, headache, malaise, and weight loss as a consequence of the decrease in CD4 T cells and the resulting immunodeficiency.[13,14] Additionally, PLWH have an increased susceptibility to ascertain other opportunistic infections. These diseases are more severe in PLWH due to the damaged immune system. Importantly, AIDS-related malignancies are the main cause of death in PLWH.[15,16] Therefore, to protect PLWH against AIDS symptoms and opportunistic infections, it is of importance to treat PLWH with anti-HIV therapies.

1.4 Highly active antiretroviral therapy (HAART)

After the HIV genome was sequenced, its three accompanying enzymes were quickly identified as primary therapeutic targets: reverse transcriptase, protease and integrase.[2,5] In the early 90s, in search of an HIV/AIDS treatment, the first small molecules to treat HIV infections were approved by the Food and Drug Administration (FDA).[17–19] Azidothymidine (AZT), previously used as an anti-cancer drug, is able to inhibit HIV reverse transcriptase. This led to AZT becoming the first approved drug to treat HIV infection in 1987.[2,17,19] Over the years, more categories and corresponding drugs were discovered for anti-HIV treatment (**Supplementary Table 1**). Antiretroviral drugs prescribed to HIV patients contain different categories: nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), integrase strand inhibitor (INSTI) and entry inhibitors (**Figure 1**).[7,17,20–23] These drugs intervene in different stages of the molecular infection pathway and lead to increased CD4+ cell count. NRTIs resemble dNTPs, yet they lack the 3'-hydroxyl group which functions as a chain terminator when it gets incorporated into the viral – newly synthesized – DNA.[7] On the other side of reverse transcription, NNRTIs directly bind the viral RT thereby inhibiting its activity.

INSTIs block the active site, hence preventing the interaction between the viral integrase and the viral DNA.[20,21] Protease Inhibitors target the HIV-protease to prevent maturation of the infectious viral particles.[22,23] In the early days of HIV treatments, only AZT was prescribed. This quickly gave rise to drug-resistant HIV variants.[2,7] Therefore, the anti-HIV drug regimen most often consists of two NRTIs in combination with a drug in another (**Supplementary Table 2**).[3,19] This therapy is named highly active antiretroviral therapy (HAART), also often called combined antiretroviral therapy (cART). HAART is now recommended for all PLWH, regardless of their CD4 cell count. By restoring immune function, HAART extends the lifespan in PLWH compared to untreated PLWH.[3,16,24]

1.5 Current status HIV-related malignancies

Even with the arrival of HAART, mortality in PLWH remains high with malignancies as its main contributor.[15,16] Additionally, the cancers are more aggressive and the age for cancer onset is lower for PLWH compared to the general population.[9,25,26] HIV-related malignancies can be divided into two categories: the AIDS-defining cancers (ADCs) and the non-AIDS-defining cancers (NADCs).[8,9] ADCs include Kaposi sarcoma (KS), Non-Hodgkin lymphoma (NHL) and invasive cervical cancer (ICC). Historically, if one of the ADCs was present in HIV-positive people one was considered to have progressed to AIDS. The increase in ADC is strongly associated with immunodeficiency, as lower CD4+ T cell counts correlate to higher ADC incidence.[27] When comparing cancer incidences pre-HAART (from 1991 – 1995) to post-HAART (from 1996 onwards), the change in ADCs and NADCs was reversed: ADCs decreased by threefold whereas NADCs had a threefold increase.[28] Over time, the NADC burden has surpassed the burden of ADCs. [27,29,30] The underlying cause of the rise of NADCs is difficult to elucidate. Therefore, this review will first identify the risks for developing cancer in PLWH, followed by an analysis of the possible contributors to the HIV patients' altered cancer burden.

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2. CANCER INCIDENCES IN PLWH

2.1 Cancer incidence in PLWH is higher

Cohort studies can yield valuable insights into the relationship between AIDS and cancer. These studies utilize record-linkage methods to generate cancer statistics in PLWH. They make use of an HIV/AIDS registry and match the records to a cancer registry. In these studies, the relative risk per cancer type is reported as a standardized incidence ratio (SIR) or the incidence rate per 100,00 person-years. The SIR is the relative risk ratio between group A in comparison to group B, e.g. PLWH compared to the general population. Cancer incidence per person-years is defined as the number of cancer diagnoses in a population, divided by the total time that population is followed, multiplied by the number of people that are studied. Most importantly, these cohort studies use the cancer incidences found in the registries to calculate a relative risk ratio of developing the malignancy for PLWH.

Even though the cohort studies tend to be heterogeneous, they do share a consensus: cancer is more prominent in PLWH compared to the general population.[31–37] KS has the highest risk ratio in PLWH, with SIRs above 100, followed by NHL with SIRs above 10 and then ICC with SIRs between 5 and 10 (**Table 1**).[35–39] The NADCs can be divided into two categories: virus-related NADCs (VRNADC) and virus-unrelated NADCs (VUNADC). In general, the VRNADCs are more prevalent in PLWH, thus have a higher relative risk ratio. This is especially seen in anal cancer, Hodgkin lymphoma (HL) and liver. These often result from an infection with e.g. Hepatitis B/C virus or Human Papillomavirus. However, also some virus-unrelated NADCs (VUNADC) were increased for PLWH. Among them are lip and lung cancer. When looking at the different cohort studies, a lot of variation can be seen in the SIRs for the different cancer types.

Multiple cohort studies have provided evidence for a higher cancer burden in PLWH compared to the HIV-negative control groups. However, cohort studies are difficult to compare. There are differences in group sizes, area and time periods. When there is a relatively small group size (e.g. a few thousand people), the SIR is accompanied by a very large confidence interval which weakens the argument raised by the SIR. Even though the risk for developing certain cancer can be estimated to be 2 or 3, the confidence interval that comes with it can be in a range of 0.6 to 80.[16,31,32,36] The demographics have changed since the introduction of HAART and varies in each cohort study, especially for the distribution of age, gender, sexual orientation, smoking, intravenous drug users (IDU).[25,32,40–43] A study has shown that 10% of the PLWH in low- and middle-income countries are above 50 years old, whereas in high-income countries this percentage is around 30%.[41] These characteristics can individually influence cancer incidences and it is not always disclosed whether these are taken into account when calculating the SIRs per cancer type (e.g. whether there is a correction for heavy smokers for the incidence of lung cancer). Additionally, HIV/AIDS-related events can vary throughout the years. This starts with changing demographics, but also the advent of HAART.[40,41] An example is an increased percentage of HIV-

positive men aged 50 years or older: from 8.5% in 1993 towards 42% in 2012. Hence, similar timeframes are preferred when comparing the results of cohort studies.

The importance of gender distribution can be seen in a study by Calabresi et al. (2013) in which they analysed a group of PLWH in Italy and determined the risk ratios for males and females separately.[36] With all cancer types taken together, the SIR is twice as big for males compared to females. Nonetheless, there is a lot of variation when looking at specific cancer types. For both tongue cancer and liver cancer, the SIR in females was threefold higher than for males. Whereas for lung cancer, this difference was the opposite way.

Table 1. Standardized incidence ratio (SIR), and their corresponding 95%-confidence interval, per cancer type and cohort study. NA = not available. Dark green = SIR > 25, middle-green = SIR > 5, light green = SIR >1 in which the 95%-CI is also above 1. Grey cells cannot give a conclusion and light orange indicates a SIR below 1.

	Clifford et al. (2005) [41]	**Mbulaiteye et al. (2006)**[36]	**Calabresi et al. (2013)**[31]	**Chen et al. (2014)**[42]	**Hernández-Ramírez et al. (2017)**[39]	**Hessol et al. (2018)**[40]
Country	Switzerland	Uganda	Italy	Taiwan	USA	USA
Cohort size	7304	12607	5090	15269	448258	22623
Time period	1985 – 2001	1988 – 2002	1999 – 2009	1998 – 2009	1996 – 2012	1990 – 2010
All ADCs	NA	**4.6** (3.8 - 5.4)	**31** (26.8 - 35.6)	NA	**13.97** (13.63 - 14.32)	NA
KS	**192** (170 - 217)	**5.7** (4.6 - 6.8)	**133.2** (109.1 - 162.7)	**298.04** (258.16 - 343.85)	**498.11** (477.82 - 519.03)	**127** (121 - 132)
NHL	**76.4** (66.5 - 87.4)	**3.6** (1.2 - 8.4)	**21.1** (17.2 - 25.7)	**26.12** (22.78 - 29.90)	**11.51** (11.14 - 11.89)	**17.2** (16.1 - 18.4)
ICC	**8.0** (2.9 - 17.4)	**2.7** (1.8 - 4.0)	**7.3** (3.8 - 14.1)	**13.95** (9.35 - 20.09)	**3.24** (2.94 - 3.56)	**8.0** (3.1 - 11.9)
All NADCs	**2.8** (2.3 - 3.3)	**2.8** (2.1 - 3.6)	NA	NA	**1.21** (1.19 - 1.23)	NA
VRNADC						
Anal	**33.4** (10.5 - 78.6)	**0** (0 - 3.5)	**42.1** (17.5 - 101.2)	**19.1** (12.80 - 27.50)	**19.06** (18.13 - 20.03)	**46.7** (39.7 - 53.6)
HL	**17.3** (10.2 - 27.4)	**5.7** (1.2 - 17)	**21.8** (15.4 - 31)	**9.35** (4.83 - 16.36)	**7.70** (7.20 - 8.23)	**10.4** (8.4 - 12.5)
Liver	**7.0** (2.2 - 16.5)	**2.1** (0.4 - 6.0)	**9.6** (6.9 - 13.4	**5.5** (4.54 - 6.59)	**3.21** (3.02 - 3.41)	**3.0** (2.3 - 3.7)
VUNADC						
Lip	**4.1** (2.1 - 7.4)	**0** (0 - 13)	NA	**8.54** (3.13 - 18.62)	**2.35** (1.43 - 3.62)	**3.8** (1.3 - 6.2)
Lung	**3.2** (1.7 - 5.4)	**5.0** (1.0 - 15)	**3.4** (2.3 - 5.1)	**8.52** (6.82 - 10.63)	**1.97** (1.89 - 2.05)	**1.3** (1.1 - 1.6)
Breast	**1.4** (0.5 - 3.4)	**1.9** (0.8 - 3.7)	NA	**0.59** (0.41 - 1.03)	**0.63** (0.58 - 0.68)	**0.74** (0.43 - 1.06)
Prostate	**1.4** (0.3 - 4.3)	**2.9** (0.3 - 11)	**1.1** (0.5 - 2.3)	**3.48** (2.03 - 5.57)	**0.48** (0.46 - 0.51)	**0.56** (0.46 - 0.66)
Brain	**2.9** (0.8 - 7.6)	**4.4** (0.1 - 24)	**1.1** (0.3 - 4.3)	**8.28** (5.59 - 11.84)	**0.57** (0.45 - 0.70)	**1.01** (0.53 - 1.49)

The study done by Clifford et al. utilized a Swiss HIV cohort study and cancer registries to calculate SIRs for different cancer types in PLWH for different conditions.[38] One of these analyses was the SIR for PLWH untreated and treated with HAART before cancer diagnosis. This shows that in absence of HAART, the cancer incidences dramatically increased with the ADCs in particular. Whereas the NADCs showed an increased SIR in HAART-treated PLWH, especially for HL.

2.2 Increase for relative risk ratio NADCs pre- to post-HAART

After the introduction of HAART in 1996, cancer incidences and the relative risk ratios have changed for PLWH. The absolute cancer incidences have increased over the years, due to the increasing number of PLWH. Therefore, the SIR is essential to be able to compare different time periods. As previously mentioned, NADCs had a threefold increase in contrast to the threefold decrease of ADCs.[28,44–46] Several cohort studies have calculated SIRs for separate periods, from pre-HAART to post-HAART, demonstrating this change in cancer development upon treatment of HAART. Nonetheless, similar to the aforementioned SIRs for the different cancer types, there is variation in both the SIRs as well as the rate at which the SIRs change from the pre- to post-HAART time periods (**Table 2**).

Table 2. Standardized incidence ratio (SIR), and their corresponding 95%-confidence interval, per cancer type and cohort study. NA = not available. Dark green = SIR > 25, middle-green = SIR > 5, light green = SIR >1 in which the 95%-CI is also above 1. Grey cells cannot give a conclusion and light orange indicates a SIR below 1.

	Engels et al. (2008)		**Powles et al. (2009)**			**Hleyhel et al. (2013)**				**Wong et al. (2022)**				
Country	USA		UK			France				Australia				
Cohort size	53750		11112			99309				28703				
Time period	1991 – 1995	1996 - 2002	1983 – 1995	1996 – 2001	2002 – 2007	1992 – 1996	1997 – 2000	2001 – 2004	2005 – 2009	1982 - 1995	1996 - 1999	2000 - 2004	2005 - 2008	2009 - 2012
ADC														
KS	**2800** (2300 - 3500)	**790** (640 - 980)	NA	NA	NA	**787.0** (754.1 - 821.0)	**388.1** (353.3 - 425.4)	**408.6** (369.6 - 450.6)	**304.5** (273.9 - 337.6)	**19024.47** (17860.02 - 20244.91)	**3826.7** (3273.07 - 4447.15)	**1027.30** (822.83 - 1257.17)	**617.39** (471.14 - 794.71)	**454.45** (345.08 - 587.48)
NHL	**9.8** (7.7 - 12)	**6.5** (5.4 - 7.7)	NA	NA	NA	**116.7** (109.9 - 123.9)	**33.6** (30.8 - 36.6)	**15.4** (13.9 - 17.1)	**9.1** (8.3 - 10.1)	**64.76** (29.14 - 70.77)	**23.82** (20.29 - 27.80)	**8.45** (6.96 - 10.16)	**4.96** (3.82 - 7.18)	**3.25** (2.56 - 4.07)
ICC	**3.1** (1.1 - 6.7)	**2.9** (1.8 - 4.4)	NA	NA	NA	**12.2** (8.7 - 16.6)	**9.3** (6.9 - 12.3)	**5.4** (3.8 - 7.5)	**5.4** (4.0 - 7.0)	NA	NA	NA	NA	NA
NADC	NA	NA	**0.95** (0.58 - 1.47)	**2.05** (1.51 - 2.72)	**2.49** (2.00 - 3.07)	NA	NA	NA	NA	NA	NA	NA	NA	NA
VRNADC														
Anal	**10** (2.1 - 29)	**9.1** (5.1 - 15)	**97.92** (42.24 - 192.95)	**109.85** (56.76 - 191.88)	**141.36** (90.57 - 210.33)	NA	NA	NA	NA	**43.03** (21.48 - 76.99)	**33.71** (15.42 - 64.00)	**33.39** (21.39 - 49.68)	**31.76** (21.58 - 45.08)	**37.71** (28.33 - 49.21)
HL	**2.8** (0.9 - 6.6)	**6.7** (4.5 - 9.5)	**4.45** (1.44 - 10.37)	**11.06** (4.78 - 21.80)	**32.35** (20.27 - 48.98)	NA	NA	NA	NA	**5.88** (3.04 - 10.26)	**10.98** (6.01 - 18.43)	**7.42** (4.06 - 12.45)	**9.90** (6.13 - 15.14)	**9.58** (6.31 - 13.93)
Liver	**0** (0.0 - 5.9)	**3.1** (1.7 - 5.2)	**0.00** (0.00 - 14.09)	**5.93** (0.72 - 21.41)	**7.00** (1.91 - 17.93	NA	NA	NA	NA	**0.85** (0.02 - 4.76)	**2.69** (0.73 - 6.89)	**2.23** (1.02 - 4.24)	**1.68** (0.84 - 3.00)	**1.94** (1.22 - 2.94)
VUNADC														
Lip	NA	NA	NA	NA	NA	NA	NA	NA	NA	**1.81** (0.83 - 3.44)	**1.75** (0.70 - 3.60)	**1.32** (0.57 - 2.61)	**0.73** (0.20 - 1.86)	**1.04** (0.45 - 2.05)
Lung	**2.6** (1.6 - 4.1)	**2.6** (2.1 - 3.2)	**0.00** (0.00 - 1.52)	**3.10** (1.34 - 6.11)	**2.37** (1.14 - 4.36)	NA	NA	NA	NA	**0.56** (0.26 - 1.06	**0.83** (0.41 - 1.48)	**0.76** (0.46 - 1.17)	**0.50** (0.29 - 0.79)	**0.82** (0.58 - 1.11)

A study by Wong et al. has analysed a group of PLWH in Australia and calculated the SIRs pre-HAART and different time periods post-HAART.[45] The drastic decrease of ADCs is shown: especially for Kaposi sarcoma starting with a SIR of 19024 pre-HAART towards a SIR of 454 in 2009-2012. A similar pattern was seen in NHL. For the NADCs, the SIR of anal cancer did not change whereas liver cancer and HL were doubled in relative risk from 1982 to 2012. Intriguingly, lung cancer had a SIR below 1. This suggests that PLWH were at a lower risk of developing lung cancer. Especially the VRNADCs have an increase, HL and anal cancer in particular. The study by Wong et al. reported a change in SIR from 5.9 to 9.90 from 1982 towards 2008. Yet, a study by Powles et al. reported a six-fold difference between 1983 and 2007.[47]

A study published in 2011 by Shiels et al. has described the cancer burden of PLWH in the United States by calculating the incidence rates per 100,000 person-years.[28] The total number of cancers has declined after 1991 but remained stable after 1997/1998, which is in contrast with the previously discussed cohort studies. The incidence rate for HL was constant, even though the absolute cancer incidence of HL tumours increased. This difference between the incidence rate and the total number can be explained by the increase in total numbers of PLWH from 1991 onwards.

Taken together, the advent of HAART affected the relative risks for both ADC and NADC development. Upon restoration of the immune system, the relative risk for ADCs significantly declines while simultaneously the relative risk for NADC development had an increase. In general, the NADCs had almost a threefold increase. When looking at the individual cancer types there was some variety, also per cohort study.

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3. RISK FACTORS FOR INCREASE IN NADC

3.1 Behavioural risk factors

Establishing the cause for the increase in NADCs is not straightforward. Multiple risk factors for NADC development are described in literature, starting with behavioural risk factors. In general, PLWH are more prone to lead lifestyles associated with increased cancer risk. Some of these lifestyles that are more present in PLWH are overweight, poor nutrition, smoking, drinking and drug abuse.[48,49] Aside from substance abuse, IDUs are even more high-risk due to sharing of the needle, as this provides blood exchange through which infections can be passed.[2] The percentage of IDUs generally make up 30-50% of the PLWH population in cohort studies, especially for countries like the USA and Australia.[16,28,31,35,36] Another high-risk behaviour is smoking, which can lead to lung cancer development. There is variation in SIRs for lung cancer in PLWH, but it is generally linked to excessive smoking behaviour. Nevertheless, some studies focused on lung cancer in which heavy smoking was taken into account when calculating the SIR. These studies have shown that even after correction, PLWH still had a SIR of 3.5.[50,51] Unfortunately, as the information on lifestyle is often not provided, it is difficult to implement this in the calculations for the SIRs in the cohort studies.

3.2 Extended life expectancy for PLWH

A partial explanation for the rise in NADC incidence is the increased lifespan for PLWH. However, cancer incidence increases exponentially with age.[9] Therefore it is required to include age distribution in the analysis, especially when comparing with the general population. As previously mentioned, almost the majority has reached an age of 50 years or older whereas thirty years ago this was less than 10%. With a higher average age comes a shift in the cancer spectrum.

3.3 Immunodeficiency and cancer

HAART can partially reconstitute the levels of $CD4^+$ in the bloodstream. However, this generally raises it to 300-400 CD4 cells/µL which is still below the level of HIV-negative people.[12] This increase in $CD4^+$ cells is correlated to the decrease in ADCs, whereas for NADCs the correlation is more variable.[9] $CD4^+$ cells play different key roles in anti-tumour activity by the immune system.[52] These cells assist other immune cells, such as the $CD8^+$ cytotoxic T lymphocytes and B-cells. Additionally, they can directly exert anti-tumour activity towards tumour cells. Thus, normally the immune system recognizes tumour tissue by the presence of neoantigens and subsequently destroys the cancer cells. Yet, upon depletion of $CD4^+$, it is easier for malignancies to progress and escape the T-cell immunosurveillance.[9,12,52] This increased risk of cancer is not only postulated for PLWH, but for every immunodeficiency disorder.[9] HIV disrupts the immune system by depleting lymphocytes, blocking lymphocyte function, increasing the secretion of cytokines subsequently leading to chronic inflammation. Even with HAART treatment, these immunologic defects are still present in PLWH.[53,54]

A by-product of immunodeficiency is the impaired control of oncogenic viruses, subsequently promoting the replication cycle of these viruses. Thus, infection of an oncogenic virus can have a more dramatic in PLWH compared to the general population. The most common co-infections in PLWH are Human papillomavirus, Hepatitis B or C virus and Epstein-Barr virus.[25,55] These three viruses are known to have a carcinogenic effect and are linked to some specific cancer types (**Table 3**).[25,55,56] NADCs can be split up into virus-related and virus-unrelated, however, virus-related cancers do not solely develop in the presence of a virus.[56] Cohort studies that include co-infections in the analyses are needed to distinguish the increase in NADC risk as a result of these co-infections and the increased risk due to other factors.

Table 3. virus-related NADC in PLWH

Virus	**Virus-related NADC**[25,55,57]
Epstein-Barr virus	Hodgkin lymphoma, Nasopharyngeal carcinoma, gastric carcinoma, NHL subtypes (e.g. Burkitt lymphoma)
Hepatitis B/C virus	Liver cancer
Human papillomavirus	Genital cancers (cervical, anal, vaginal, vulva, penis), head and neck cancer

3.4 Potential carcinogenesis of HAART

Over the past three decades, the FDA has approved multiple drugs to treat HIV infections. These drugs have successfully improved the quality of life for PLWH. However, some HAART drugs might play a role in cancer development and cancer progression. Multiple studies have established a link between antiviral drugs and mutagenicity.[58–61] Most evidence is found for NRTIs, which are the backbone of therapy for HIV.[62] Here we will focus on a few NRTIs, the INSTI raltegravir and protease inhibitors.

AZT is the most studied NRTI. In 1998, pregnant women taking AZT were studied, both HIV-positive and HIV-negative women.[61] AZT was found to be incorporated into the DNA of both adults and infants, yet the biological consequences of these events were not known. A study in 2007 was conducted in male mice and human lymphoblastoid cells upon treatment with AZT, lamivudine and abacavir.[58] The mutagenicity was studied by analysing the mutant frequencies in reporter genes, such as the HPRT and TK genes. It was found that co-exposures of AZT-lamivudine yielded an increase in HPRT and TK mutant frequencies. A similar experimental setup was used in another study in 2007.[59] This study also involved two drugs that are no longer on the market in the US: didanosine and stavudine. Significant elevation in HPRT mutants was found for combinations of AZT, didanosine and/or lamivudine. The potential genotoxic effects for abacavir, lamivudine and AZT treatment were measured in *D. Melanogaster* in a study in 2019.[60] Here it was stated that the genotoxicity was predominantly caused by recombination events instead of mutations. HAART-induced DNA recombination could stimulate carcinogenesis, e.g. by gene fusion of cancer driver genes or inactivation of tumour suppressor genes.[60]

A study in 2013 has linked the INSTI raltegravir to aberrant integration of the HIV-1 viral DNA as well as genome rearrangements of the host cells.[63] The latter could potentially activate oncogenes and/or inactivate tumour suppressor genes.[20] However, a cohort study was done to analyse the incidence of cancer in PLWH that are receiving raltegravir or not as HAART.[24] This study has not found a significant correlation to cancer onset or progression when using raltegravir compared to the control groups.

Contrastingly, most PIs prescribed to treat HIV infection convey an anti-tumour activity. A few examples are ritonavir and nelfinavir. Ritonavir is reported to kill bladder cancer cells by accumulating ubiquitinated proteins and is able to induce cytotoxicity in acute myeloid leukaemia cells.[64,65] Additionally, Nelfinavir has been used as an anticancer agent in a broad range of cancer types, such as multiple myeloma and bladder cancer, as a result of cell cycle arrest, cell death and endoplasmic reticulum stress.[66–68]

As previously mentioned, the resistance of HIV towards antiretroviral drugs is quickly obtained upon administering a single drug setting combination therapy as standard.[2] Therefore, it is needed to study the ART drugs in combination, as drug-drug interactions could influence mutagenic potential. Cimduo is the trade name for a combination therapy containing two NRTIs. This drug was found to be increasing the micronucleus frequency, which is generally considered a biomarker of genomic instability and carcinogenesis.[69,70] However, there was no difference seen in micronucleus frequency between PLWH untreated and treated with an NRTI-based drug regime.[70] This suggests that enhanced micronucleus frequency could be caused by the HIV infection rather than an NRTI-based HAART treatment.

4. DISCUSSION

The burden of cancer is not only higher for PLWH compared to the general population, it is also the primary cause of death for PLWH. Cohort studies compared the HIV-positive population with the general population, to calculate the relative risk ratios per cancer type. These relative risks have changed after the introduction of HAART in which ADC risk has substantially decreased whereas NADCs had an increase. Statistics of the relative risk ratios per cancer type and the probable contributors for cancer development are discussed in this review.

4.1 Cohort heterogeneity

There is a high degree of heterogeneity when examining the different cohort studies. There is a consensus among the different cohort studies regarding the decrease in ADCs and the increase in NADCs. However, there are some discrepancies when looking at the relative risk ratios per cancer type. The variation in SIRs can, at least partially, be explained by the diversity in cohort characteristics. These involve cohort size, statistical measures and demographics. To begin with, the size of the cohort affects the validity of the study: even though the risk for developing certain cancer can be estimated to be 2 or 3, the confidence interval that comes with it can be in a range of 0.6 to 80.[16,31,32,36] Nevertheless, the confidence intervals are not always indicated in concluding remarks in the study. In smaller cohorts, it can happen that two cases of a specific cancer type were seen whereas the expected number was 0.5. This already leads to a relative risk ratio of 4, even though these two cases could have happened at random. The bigger the cohort size, the more accurate and trustworthy the result. The statistical analysis to determine the cancer burden in PLWH is approached differently across the cohort studies: SIRs, incidence per 100,000 person-years and sometimes just the absolute cancer incidences. Especially the latter could not lead to conclusions, as it does not take the group size into account. This is also seen in the study of Shiels et al. in 2011, in which the total number of cancer incidence increased over time from pre- to post-HAART whereas the calculated incidence rate per 100,000 person-years has decreased.[28] The obstacle in person-year is that there is no direct comparison with the cancer risk in the general population of the same area. Hence, it is difficult to compare the number per person-years for studies analysing PLWH in different areas as they do not normalise for cancer incidences associated with the area characteristics, instead of the HIV infection.

Group demographics are important to include in the cohort analysis, as these can contribute to the development of the different cancer types. A large difference is seen in SIRs for males and females, highlighting the importance of gender distribution of the cohort. Other demographics that could alter the cancer incidence spectrum are the percentage of males having sex with males (MSM), race, age, smoking, IDUs, and alcohol abuse. Even when this information is available for the cohort study, it is not always disclosed whether a correction was done for these demographic risk factors. Moreover, there is variation in the time periods for which the SIR analysis is performed. Some studies just look at pre-and post-HAART whereas some also separate post-HAART in early and late post-HAART. Taken together, multiple components can influence the increased relative risk for NADCs in PLWH.

4.2 Risk factors in PLWH

Reconstitution of the immunodeficiency by HAART is probably the primary cause for the decrease in ADC incidence. However, the effect of HAART in NADCs tends to be more complicated. These NADCs can be influenced by lifestyle: e.g. drug use and smoking. Co-infections could also play a key role in the development of virus-related NADCs. Nonetheless, reducing these risk factors seems not to be the only argument for preventing the onset of AIDS-related malignancies.

As NRTIs remain the base of prescribed HAART drugs, it is important to elucidate its potential backlash on the quality of life by promoting carcinogenesis. In a lab setting, different HAART drugs were linked to mutagenic events or inducing genomic instabilities. Pursuing these kinds of experiments with the different drugs, with longer exposure times is needed to get a better understanding of what these drugs could do to the healthy cells in PLWH. What is the damage on a small scale? What cell line fits the experiment best, considering the cell line's genetic background? Does the drug cause mutagenesis through an increase in HPRT/TK reporter genes? Is there an increase in genomic instability for specific drugs, or drug types? Does the drug promote selection which cancer cells can escape from whilst healthy cells will be destroyed? These are questions that need to be addressed when analysing the different antiviral drugs given to HIV patients. For a larger-scale analysis, there is a need for cohort studies that include the prescribed drugs for the registered PLWH. These studies also need to incorporate the group demographics (e.g. age, gender, lifestyle) and the presence of co-infections. Ideally, information on the specific prescribed drugs is included in the cohort study to identify associations between individual drugs and

cancer types. Unfortunately, in the first place, this information is not always listed in the HIV registries. It is difficult to include all the aforementioned components, yet it can provide vital information for the potential risk factors on patient level.

Taken together, there are a lot of different risk factors that can affect tumour development. These risk factors need to be included in cohort studies to determine their independent contributions. Aside from lifestyle and co-infections, the prescribed drugs can stimulate AIDS-related malignancies. Especially the long-term safety of the antiviral drugs are not fully known for PLWH. These drugs are vital for PLWH, improve quality of life and extend their life expectancy. However, potential mutagenic or genotoxic side effects of these drugs must be detected as the PLWH have to take them on a daily basis. The extended knowledge of potential damage for healthy cells can be used to further improve HIV drug regimes and diminish adverse effects coming from these drugs.

LAYMAN'S SUMMARY

Humaan immunodeficiëntie virus (HIV) is ontdekt in het begin van de tachtigerjaren en binnen tien jaar was al het eerste antivirale medicijn goedgekeurd door de medicijnagentschappen. De voornaamste doodsoorzaak van HIV-patiënten is het overlijden aan kanker. Voor dat de medicijnen voor HIV infecties op de markt waren, was dit vooral een zeldzame soort bloedvatkanker (Kaposi sarcoom), lymfeklierkanker (non-hodgkinlymfoom) en baarmoederhalskanker. Echter, sinds de komst van de medicijnen zijn de type kankers die voorkomen bij HIV-patiënten veranderd. Hiervoor zijn meerdere oorzaken, die allemaal onafhankelijk invloed kunnen hebben op tumorontwikkeling. In deze review worden de verschillende oorzaken uiteengezet.

HIV valt een bepaald type witte bloedcel aan: de CD4-cellen. Hierdoor neemt het totale aantal CD4-cellen in je bloed af, terwijl deze nodig zijn voor het afweermechanisme tegen HIV. HIV valt juist die cellen aan die nodig zijn om HIV eigenlijk weer 'op te ruimen'. Echter, die antivirale medicijnen die HIV-patiënten krijgen, verhogen dus onder andere het aantal CD4-cellen in je bloed. Hierdoor is je lichaam ook weer iets beter bestand tegen andere infecties en ziektes. Want als je immuunsysteem plat ligt, krijgen tumoren ook meer de kans om te ontwikkelen en te groeien. Dit kan in eerste instantie verklaren waarom er zo een verandering is in type kankers die voorkomen bij HIV-patiënten.

Onder de HIV-patiënten is er een verhoogd aantal rokers en alcoholisten. Dit brengt ook risico's met zich mee: roken kan leiden tot longkanker, overmatig alcohol gebruik kan onder andere leiden tot leverkanker. Verder zijn HIV-patiënten ook vatbaarder voor co-infecties met andere virussen: zoals humaan papillomavirus (HPV) wat onder meer baarmoederhalskanker kan veroorzaken.

Echter is het ook van belang om bijwerkingen van de antivirale medicijnen te detecteren, om zo te achterhalen wat er eventueel verbeterd kan worden bij deze medicijnen. Antivirale medicijnen die bedoeld zijn om HIV en geïnfecteerde cellen te beschadigen, kunnen deze beschadigingen ook veroorzaken in gezonde cellen. De schade in deze gezonde cellen kan op hele kleine schaal plaatsvinden, zoals bijvoorbeeld door mutaties in het DNA of genetische recombinatie. Meerdere studies hebben laten zien dat dit mogelijk is, vooral de medicijnen die de reverse-transcriptase (die het HIV RNA omzet in DNA) afremmen. Deze schade kan uiteindelijk een trigger zijn voor kankerontwikkeling, bijvoorbeeld wanneer er een gen wordt uitgeschakeld die nodig is om de kanker te onderdrukken.

Aangezien HIV patiënten deze medicijnen vrijwel dagelijks moeten slikken is het belangrijk om de mogelijke bijwerkingen op het DNA te blijven onderzoeken. Voor de veiligheid van de medicijnen op langere termijn is het van belang dat er grote cohort studies worden gedaan waarbij wordt gekeken naar de type kankers van HIV patiënten, inclusief welke medicijnen er voorgeschreven zijn voor de patiënten, wat voor infecties hebben plaatsgevonden en welke schadelijke levensstijlen de patiënten hebben. Hiermee kan er wellicht een verband gevonden worden tussen een type medicijn en een type kanker.

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SUPPLEMENTARY

Supplementary Table 1. Overview of the individual antiviral drugs approved for anti-HIV treatment. * = discontinued.

Monotherapy

Drug class	Trade name	Generic name	Abbreviation	Molecule type	Year of FDA approval
Nucleoside analogue reverse transcriptase inhibitors (NRTIs)	Retrovir	Zidovudine	ZDV/AZT	Small molecule	1987
	Videx*	Didanosine	ddI	Small molecule	1991
	Hivid*	Zalcitabine	ddC	Small molecule	1992
	Zerit*	Stavudine	d4T	Small molecule	1994
	Epivir	Lamivudine	3TC	Small molecule	1995
	Ziagen	Abacavir	ABC	Small molecule	1998
	Viread	Tenofovir disoproxil fumarate	TDF	Small molecule	2001
	Emtriva	Emtricitabine	FTC	Small molecule	2003
	Retrovir	Zidovudine	ZDV/AZT	Small molecule	1987
Non-nucleoside analogue reverse transcriptase inhibitors (nNRTIs)	Viramune	Nevirapine	NVP	Small molecule	1996
	Rescriptor*	Delavirdine	DLV	Small molecule	1997
	Sustiva	Efavirenz	EFV	Small molecule	1998
	Intelence	Etravirine	ETR	Small molecule	2008
	Edurant	Rilpivirine	RPV	Small molecule	2011
	Pifeltro	Doravirine	DOR	Small molecule	2018
Protease inhibitors (PI)	Invirase*	Saquinavir mesylate	SQV	Small molecule	1995
	Crixivan*	Indinavir sulfate	IDV	Small molecule	1996
	Norvir	Ritonavir	RTV	Small molecule	1996
	Viracept	Nelfinavir mesylate	NFV	Small molecule	1997
	Agenerase*	Amprenavir	APV	Small molecule	1999
	Reyataz	Atazanavir	ATV	Small molecule	2003
	Lexiva	Fosamprenavir	FPV	Small molecule	2003
	Aptivus	Tipranavir	TPV	Small molecule	2005
	Prezista	Darunavir	DRV	Small molecule	2006
Integrase strand transfer inhibitors (INSTI)	Isentress	Raltegravir	RAL	Small molecule	2007
	Tivicay	Dolutegravir	DTG	Small molecule	2013
	Vitekta*	Elvitegravir	EVG	Small molecule	2014
	Vocabria	Cabotegravir	CAB	Small molecule	2021
Entry inhibitors					
Fusion inh.	Fuzeon	Enfuvirtide	T20	Peptide	2003
CCR5 antagonist	Selzentry	Maraviroc	MVC	Small molecule	2007
Attachment inh.	Trogarzo	Ibalizumab	IBA	Protein	2018
Post-attachment inh.	Rukobia	Fostemsavir	FTR	Small molecule	2020
Pharmacokinetic enhancers	Norvir	Ritonavir	RTV	Small molecule	1996
	Tybost	Cobicistat	COBI	Small molecule	2014

Supplementary Table 2. Overview of the comined antiviral drugs, and their trade name, approved for anti-HIV treatment. * = discontinued.

Combotherapy				
Trade name	**Generic name**	**Abbreviation**	**Drug class**	**Year of FDA approval**
Combivir	Lamuvidine/zidovudine	3TC/AZT	NRTI/NRTI	1997
Kaletra	Lopinavir/ritonavir	LPV/RTV	PI/CYP3A	2000
Trizivir	Abacavir/lamivudine/zidovudine	ABC/3TC/AZT	NRTI/NRTI/NRTI	2000
Epzicom	Abacavir sulfate/lamivudine	ABC/3TC	NRTI/NRTI	2004
Truvada	Emtricitabine/tenofovir disoproxil fumarate	FTC/TDF	NRTI/NRTI	2004
Atripla	Efavirenz/emtricitabine/tenofovir disoproxil fumarate	EFV/FTC/TDF	NRTI/NRTI/NRTI	2006
Complera	Emtricitabine/rilpivirine/tenofovir disoproxil fumarate	FTC/RPV/TDF	NRTI/NRTI/NRTI	2011
Stribild	Cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil fumarate	COBI/EVG/FTC/TDF	CYP3A/INSTI/NRTI/NRTI	2012
Triumeq	Abacavir/dolutegravir/lamivudine	ABC/DTG/3TC	NRTI/INSTI/NRTI	2014
Dutrebis*	Lamivudine/raltegravir	3TC/RAL	NRTI/INSTI	2015
Evotaz	Atazanavir/cobicistat	ATV/COBI	PI/CYP3A	2015
Genvoya	Cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide fumarate	COBI/EVG/FTC/TAF	CYP3A/INSTI/NRTI/NRTI	2015
Prezcobix	Cobicistat/darunavir	COBI/DRV	CYP3A/PI	2015
Descovy	Emtricitabine/tenofovir alafenamide fumarate	FTC/TAF	NRTI/NRTI	2016
Odefsey	Emtricitabine/rilpivirine/tenofovir alafenamide fumarate	FTC/RPV/TAF	NRTI/NRTI/NRTI	2016
Juluca	Dolutegravir/rilpivirine	DTG/RPV	INSTI/NRTI	2017
Biktarvy	Bictegravir/emtricitabine/tenofovir alafenamide fumarate	BIC/FTC/TAF	INSTI/NRTI/NRTI	2018
Cimduo	Lamivudine/tenofovir disoproxil fumarate	3TC/TDF	NRTI/NRTI	2018
Delstrigo	Doravirine/lamivudine/tenofovir disoproxil fumarate	DOR/3TC/TDF	NRTI/NRTI/NRTI	2018
Symfi	Efavirenz/lamivudine/tenofovir disoproxil fumarate	EFV/3TC/TDF	NRTI/NRTI/NRTI	2018
Symfi Lo	Efavirenz/lamivudine/tenofovir disoproxil fumarate	EFV/3TC/TDF	NRTI/NRTI/NRTI	2018
Symtuza	Cobicistat/darunavir/emtricitabine/tenofovir alafenamide fumarate	DRV/COBI/FTC/TAF	PI/CYP3A/NRTI/NRTI	2018
Dovato	Dolutegravir/lamivudine	DTG/3TC	INSTI/NRTI	2019
Cabenuva	Cabotegravir/rilpivirine	CAB/RPV	INSTI/NRTI	2021