Assessing the impact of HAART on the incidence of defining and non-defining AIDS cancers among patients with HIV/AIDS: A systematic review

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Summary  After highly active antiretroviral therapy (HAART) became widespread, several studies demonstrated changes in the incidence of defining and non-defining AIDS cancers among HIV/AIDS patients. We conducted a systematic review of observational studies evaluating the incidence of malignancies before and after the introduction of HAART in people with HIV/AIDS. Eligible studies were searched up to December 2012 in the following databases: Pubmed, Embase, Scielo, Cancerlit and Google Scholar. In this study, we determined the cancer risk ratio by comparing the pre- and post-HAART eras. Twenty-one relevant articles were found, involving more than 600,000 people with HIV/AIDS and 10,891 new cases of cancers. The risk for the development of an AIDS-defining cancer decreased after the introduction of HAART: Kaposi's sarcoma (RR = 0.30, 95% CI: 0.28–0.33) and non-Hodgkin's lymphoma (RR = 0.52, 95% CI: 0.48–0.56), in contrast to invasive cervical cancer (RR = 1.46, 95% CI: 1.09–1.94). Among the non-AIDS-defining cancers, the overall risk increased after the introduction of HAART (RR = 2.00, 95% CI: 1.79–2.23). The
Introduction

Since 1996, when highly active antiretroviral therapy (HAART) became widespread in North America, Europe and Australia, the mortality rate in HIV-infected patients dropped dramatically, mainly because of the decrease in the incidence of opportunistic infections. In addition to life expectancy, the therapy also affected the epidemiology of non-AIDS-defining cancers (NADCs) and has an important impact on the evolution of these tumors [1].

Before HAART, cancers were responsible for less than 10% of deaths among HIV-infected patients [1]. After HAART, 28% of deaths in this population have been attributed to neoplastic causes [2], despite the substantial decline in the risk of acquiring AIDS-defining cancers (ADCs), especially Kaposi’s sarcoma (KS) and non-Hodgkin’s lymphoma (NHL) [3]. It is believed that this phenomenon occurs as a function of the increase in the incidence and mortality of NADCs [4]. However, it is still not clear in the literature whether the higher incidence of carcinomas in the post-HAART era is only due to the larger number of new cases of NADCs or if there are other factors involved, such as the longer life expectancy afforded by HAART [3].

Some studies speculate that as HIV patients live longer after the introduction of HAART, there is a greater potential to develop cancers [5]. Other authors believe that the association between different risk factors, such as HIV-infection chronicity and its probable oncogenic role, may be involved [2].

In fact, despite the advances in medicine, cancer is now one of the leading causes of death among patients who live with HIV [6]. This article aims to provide a systematic review to evaluate the impact of HAART on the incidence of defining and non-defining AIDS cancers.
Methods

This study adhered to the MOOSE guidelines [7].

Inclusion criteria

Studies meeting the following criteria were included: (1) cohort studies of people with HIV/AIDS that assessed cancer incidence before and after the introduction of HAART, (2) studies including adult subjects, (3) studies published between 2001 and 2012 and (4) studies including data on the cancer incidence in person-years.

Search and selection of literature

Eligible studies were identified by searching the following databases: Pubmed, Embase, Scielo, Cancerlit and Google Scholar. The studies were identified by a literature search of the databases using the following medical subject heading terms and/or text words: “AIDS”, “HIV”, “cancer”, “HAART”, “incidence” and “cohort”. The reference lists of the identified publications were reviewed for additional pertinent studies. No language restrictions were imposed.

Three researchers (PHL, PCS and MCMC) searched for articles published prior to December 2012. After searching the databases, 2392 potentially relevant HIV/AIDS papers were identified, 2333 of which were excluded: 1929 after reviewing the title and 404 after reviewing the abstract. Three studies were included after reviewing the References.

Thus, 62 papers met the search criteria and were evaluated using the Newcastle-Ottawa scale [8]; 35 were excluded. The Newcastle-Ottawa scale evaluates the quality of cohort studies; articles that score higher than five are considered to be studies of “high methodological quality”. The scale was independently applied by two researchers (RNOC and MCMC), and any discordance was solved by a third researcher (AKSG). Six articles were excluded for repeated reporting (Fig. 1).

Data extraction

Various study characteristics were extracted from the original studies and included in the systematic review. The data included the first authors’ last names, the year of publication, the country, the study design, the period of follow up, the number of patients, the total person-years and the number of cancers (Table 1). Cancer incidence among HIV/AIDS patients in the pre- and post-HAART periods were abstracted from each study. Three blind reviewers (RNOC, MCMC and AKSG) used the inclusion criteria to choose eligible articles. Disagreements were solved by means of mutual consensus.

Analysis

Data were entered in Review Manager (RevMan) 4.2. This software allows the user to enter protocols, to complete reviews, including text, characteristics of the studies, comparison tables, and study data, and to perform meta-analyses of the data entered.

With the incidence in person-years, we determined the risk ratio for each studied malignancy using fixed and random effects models and testing for the heterogeneity of effects using the Chi-squared test in RevMan 4.2.

Results

We found 21 relevant articles involving more than six hundred thousand HIV/AIDS patients, who contributed more than two million person-years of follow-up and who were diagnosed with 10,891 new cases of cancers. The design features of the chosen studies are indicated in Table 1.

Regarding the ADCs, the beginning of HAART decreased the risk to develop KS (RR = 0.30, 95% CI: 0.28–0.33) and NHL (RR = 0.52, 95% CI: 0.48–0.56) when compared with the pre-HAART period (Figs. 2 and 3). In contrast to KS and NHL, we...
found that the risk of developing invasive cervical cancer (RR = 1.46, 95% CI: 1.09–1.94) increased after the introduction of HAART (Fig. 4).

In the articles that included data on non-Hodgkin’s lymphoma, we found that the introduction of HAART decreased the rates of non-Hodgkin’s lymphoma, especially the risk of primary brain lymphoma (RR = 0.24, 95% CI: 0.20–0.30). The risk of acquiring diffuse large B-cell lymphoma and Burkitt’s lymphoma, the two most common systemic NHL subtypes among patients with HIV/AIDS, also decreased significantly (RR = 0.44, 95% CI: 0.40–0.49 and RR = 0.44, 95% CI: 0.27–0.73, respectively).

The overall risk of developing NADCs increased after the introduction of HAART (RR = 2.00, 95% CI: 1.79–2.23), as shown in Fig. 5. However, among the cancers studied, we found a significant risk increase in a group of six malignancies: anus (RR = 4.28, 95% CI: 3.25–5.64), colorectal (RR = 1.91, 95% CI: 1.03–3.52), Hodgkin’s lymphoma (RR = 1.40, 95% CI: 1.16–1.69), liver (RR = 3.58, 95% CI: 2.57–4.99), lung (RR = 2.19, 95% CI: 1.54–3.11) and prostate (RR = 2.57, 95% CI: 1.49–4.44).

<table>
<thead>
<tr>
<th>Table 1 Cohort study design features of cancer risk in HIV/AIDS patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study, year (reference)</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Dorruchi et al., 2001 [27]</td>
</tr>
<tr>
<td>Bower et al., 2003 [29]</td>
</tr>
<tr>
<td>Hessol et al., 2004 [31]</td>
</tr>
<tr>
<td>D’Souza et al., 2008 [32]</td>
</tr>
<tr>
<td>Franceschi et al., 2008 [33]</td>
</tr>
<tr>
<td>Polesel et al., 2008 [34]</td>
</tr>
<tr>
<td>Clifford et al., 2009 [36]</td>
</tr>
<tr>
<td>Dal Maso et al., 2009 [43]</td>
</tr>
<tr>
<td>Powles et al., 2009 [41]</td>
</tr>
<tr>
<td>Buchacz et al., 2010 [37]</td>
</tr>
<tr>
<td>Franceschi et al., 2010 [42]</td>
</tr>
<tr>
<td>Seaberg et al., 2010 [40]</td>
</tr>
<tr>
<td>Besson et al., 2011 [38]</td>
</tr>
<tr>
<td>Franzetti et al., 2012 [10]</td>
</tr>
</tbody>
</table>

<sup>a</sup> RL, record-linkage.

![Figure 2](image-url)  
**Figure 2** Incidence rates for Kaposi’s sarcoma in the pre- and post-HAART eras and the risk ratios of incidence rates in the pre-HAART compared with the post-HAART era.
HAART impact on cancer incidence among HIV patients

<table>
<thead>
<tr>
<th>Study</th>
<th>pre-HAART</th>
<th>post-HAART</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cianfrone, 2009</td>
<td>255</td>
<td>125</td>
<td>0.49 [0.30, 0.79]</td>
</tr>
<tr>
<td>Dal Maso, 2009</td>
<td>741</td>
<td>781</td>
<td>1.05 [0.92, 1.21]</td>
</tr>
<tr>
<td>Leewen, 2009</td>
<td>766</td>
<td>335</td>
<td>0.44 [0.37, 0.51]</td>
</tr>
<tr>
<td>Bessou, 2011</td>
<td>860</td>
<td>429</td>
<td>0.50 [0.43, 0.58]</td>
</tr>
<tr>
<td>Kirk, 2011</td>
<td>1990</td>
<td>300</td>
<td>0.15 [0.10, 0.22]</td>
</tr>
<tr>
<td>Polesel, 2011</td>
<td>859</td>
<td>260</td>
<td>0.30 [0.24, 0.38]</td>
</tr>
</tbody>
</table>

Total (95% CI): 0.52 [0.48, 0.56]

Heterogeneity: Chi² = 163.37, df = 5 (P < 0.00001); I² = 97%
Test for overall effect: Z = 16.98 (P < 0.00001)

**Figure 3** Incidence rates for non-Hodgkin’s lymphoma in the pre- and post-HAART and the risk ratios of incidence rates in the pre-HAART compared with the post-HAART era.

<table>
<thead>
<tr>
<th>Study</th>
<th>pre-HAART</th>
<th>post-HAART</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donocci, 2001</td>
<td>70</td>
<td>469</td>
<td>6.22 [1.14, 33.92]</td>
</tr>
<tr>
<td>Hessol, 2004</td>
<td>0</td>
<td>18</td>
<td>1.38 [0.06, 33.87]</td>
</tr>
<tr>
<td>Biggar, 2007</td>
<td>64</td>
<td>86</td>
<td>1.34 [0.97, 1.86]</td>
</tr>
<tr>
<td>Engels, 2008</td>
<td>28</td>
<td>50</td>
<td>1.81 [0.68, 4.82]</td>
</tr>
<tr>
<td>Buchacz, 2010</td>
<td>400</td>
<td>600</td>
<td>1.50 [0.49, 4.64]</td>
</tr>
</tbody>
</table>

Total (95% CI): 1.46 [1.09, 1.94]

Heterogeneity: Chi² = 2.07, df = 3 (P = 0.56); I² = 0%
Test for overall effect: Z = 2.06 (P = 0.04)

**Figure 4** Incidence rates for invasive cervical cancer in the pre- and post-HAART eras and the risk ratios of incidence rates in the pre-HAART compared with the post-HAART era.

<table>
<thead>
<tr>
<th>Study</th>
<th>pre-HAART</th>
<th>post-HAART</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hessol, 2004</td>
<td>280</td>
<td>277</td>
<td>0.99 [0.40, 2.41]</td>
</tr>
<tr>
<td>Cianfrone, 2009</td>
<td>285</td>
<td>545</td>
<td>1.91 [1.39, 2.63]</td>
</tr>
<tr>
<td>Dal Maso, 2009</td>
<td>286</td>
<td>490</td>
<td>1.72 [1.40, 2.10]</td>
</tr>
<tr>
<td>Leewen, 2009</td>
<td>136</td>
<td>188</td>
<td>1.38 [1.09, 1.76]</td>
</tr>
<tr>
<td>Powles, 2009</td>
<td>70</td>
<td>316</td>
<td>4.56 [2.85, 7.29]</td>
</tr>
<tr>
<td>Francesch, 2010</td>
<td>300</td>
<td>586</td>
<td>1.96 [1.46, 2.59]</td>
</tr>
<tr>
<td>Seaberg, 2010</td>
<td>46</td>
<td>111</td>
<td>2.39 [1.39, 4.09]</td>
</tr>
<tr>
<td>Franzetti, 2013</td>
<td>101</td>
<td>450</td>
<td>4.41 [2.87, 6.79]</td>
</tr>
</tbody>
</table>

Total (95% CI): 2.00 [1.79, 2.23]

Heterogeneity: Chi² = 39.10, df = 7 (P < 0.00001); I² = 82%
Test for overall effect: Z = 12.16 (P < 0.00001)

**Figure 5** Incidence rates for non-AIDS-defining cancers in the pre- and post-HAART eras and the risk ratios of incidence rates in the pre-HAART compared with the post-HAART era.
However, we did not find a statistically significant increase or decrease in the development of the following NADC types after the initiation of HAART: bladder (RR = 1.88, 95% CI: 0.59–6.00), CNS (RR = 1.81, 95% CI: 0.86–3.85), kidney (RR = 1.79, 95% CI: 0.72–4.44), leukemia (RR = 0.84, 95% CI: 0.44–1.60), melanoma (RR = 1.08, 95% CI: 0.71–1.65) and testis (RR = 0.84, 95% CI: 0.38–1.89).

Discussion

Non-AIDS-defining cancers (NADCs)

Several theories attempt to explain the increasing importance of NADCs among HIV-infected patients. Although some studies have demonstrated a direct relationship between HAART and increased incidence of NADCs [4], it is more likely that antiretroviral therapy indirectly affects the epidemiology of these cancers because HAART increases the life expectancy of people living with HIV, thus allowing the emergence of these carcinomas [4].

Another possibility is that the genomic instability caused by zidovudine may contribute to the increased incidence of certain types of NADCs. The first nucleoside reverse transcriptase inhibitors (NRTIs) approved for the therapy of HIV is incorporated into DNA, causes mutations in the hypoxanthine-guanine phosphoribosyl-transferase (HPRT) and thymidine kinase (TK) genes, and induces micronuclei, chromosomal aberrations, sister chromatid exchange, shortened telomeres, and other genotoxic effects in cultured cells [9].

Anal cancer

There is a proven association between anogenital cancers and infection by human papilloma virus (HPV), and we also know that patients living with HIV have a higher incidence of HPV infection, especially of high-risk strains [10]. We found a fourfold increase in the risk for developing anal cancer in the post-HAART era (RR: 4.28, 95% CI: 3.25–5.64). Our finding was similar to the results found by Legarth et al. in 2013 (RR: 77.9, 95% CI: 36.2–167.7) [11]. This fact can be explained partly by the fact that the use of HAART does not reduce the incidence of anogenital cancer precursor lesions and it does not seem able to eliminate HPV infection [10]. Furthermore, the recommendations of performing screening for anal cancer and its precursors in the population with HIV can lead to an increase in the number of diagnoses [12]. Recently, a multicenter study showed that the use of HAART was associated with a lower prevalence of anal intraepithelial neoplasia (AIN) and a lower prevalence of HPV infection [13]. However, this study has some limitations that should be highlighted, including its cross-sectional design. Additionally, the article does not address the effect of HAART on high-grade anal intraepithelial neoplasia (HGIN) specifically, as the size of the study was limited and only a small proportion of those with AIN had HGAIN [14].

Hodgkin’s lymphoma

Hodgkin’s lymphoma (HL) is a common malignancy among patients with AIDS, congenital immunodeficiency syndromes or those under immunosuppressive drug regimens. This fact suggests that immunosuppression is directly related to the pathogenesis of HL; however, the relationship is much more complex and multifactorial [15]. We found an increased risk for developing HL after HAART (RR: 1.40, 95% CI: 1.16–1.69) that was similar to the standardized incidence ratio (SIR) found by Clifford et al. in 2005 (pre-HAART SIR = 17.3 compared to post-HAART SIR = 36.2) [16] and Herida et al. in 2003 (pre-HAART SIR 22.75 compared to post-HAART SIR = 31.66) [17]. In addition to the substantial increase in the age of the population living with HIV after the introduction of HAART (from 34.2 years to 42.8 years) [16], the increased incidence is related to immune reconstitution: it is known that the incidence of HL decreases with severe immunosuppression and increases with moderate immunosuppression [15]. It is also known that HL is strongly associated with Epstein–Barr virus (EBV) infection and that immune reconstitution increases the stimulation of B cells, thereby increasing the number of lymphocytes infected with EBV [15].

Liver cancer

In general, the incidence of liver cancer is increased in patients with HIV/AIDS. Some studies suggest that this difference may result from a greater prevalence of infection by hepatitis B virus (HBV), and especially hepatitis C virus (HCV) [18]. The co-infection of HIV and HBV or HCV seems to increase the risk of cirrhosis, end-stage renal disease and hepatocellular carcinoma. Our statistical analysis found that the risk for developing liver cancer after HAART increased more than three times compared to the pre-HAART risk (RR: 3.58, 95% CI: 2.57–4.99), similar to what was found by Sahasrabuddhe et al. in 2012, (RR = 2.50, 95% CI: 1.70–3.70) [18]. The main reason for the higher risk is the increase in
survival of people living with HIV/AIDS after the introduction of HAART; in addition, it is suspected that the hepatotoxicity of HAART may worsen the carcinogenic effect of hepatitis B and C [18].

**Lung cancer**

Many studies indicate that lung cancer is the most common NADC in the HIV-infected population, in both the pre- and post-HAART eras. As smoking is the main risk factor for the development of lung cancer, we established the relationship between the increased incidence of this tumor with the highest rate of smoking in the HIV-infected population; in fact, 35–70% of people living with HIV/AIDS smoke, while only 20% of the general population are smokers [19]. However, other factors also appear to be related to the increased incidence of lung cancer in these patients because the risk remains high even after correcting for smoking status [10]. Although some studies do not show a statistically significant increase in the risk of developing lung cancer after HAART [10,20], our study found a doubling of the pre-HAART era risk in the post-HAART era (RR: 2.19, 95% CI: 1.54–3.11), and this result is similar to what was found by Polese et al. in 2010 (RR: 1.8, 95% CI: 1.00–3.2) [21]. The increased risk may be explained in part by the long period from the acquisition of HIV until the diagnosis for lung cancer (11 years on average in the post-HAART era). Thus, studies in the pre-HAART era, when the life expectancy of the HIV-infected population was much lower than that of the post-HAART era, made no diagnoses of lung cancer simply because the patients died from other causes first, mainly opportunistic infections and AIDS-defining cancers [19].

**Prostate cancer**

Although we found an increased incidence of prostate cancer in the post-HAART era (RR: 2.57, 95% CI: 1.49–4.44), very few of the published studies included this outcome, so we cannot clearly determine the direction of this neoplasm in HIV-positive patients. Moreover, among the few articles that address prostate cancer, the samples studied are small and thus not able to detect significant differences [10]. In 2009, Silberstein et al. [22] suggested that HAART may be a protective factor against prostate cancer. However, in 2008, Pantanowitz et al. [23] showed that in a cohort study, 82% of men diagnosed with prostate cancer were receiving HAART. We know that the risk of developing prostate cancer is associated with the age and origin of the patients; moreover, the presence or absence of a screening program substantially alters the incidence of this neoplasia. Many articles [10,22,23] showed that the incidence of prostate cancer in patients living with HIV/AIDS may be equal, lower or even higher than that of the general population, which highlights the need to perform more studies before definitive conclusions can be reached.

**AIDS-defining cancers (ADCs)**

**Kaposi’s Sarcoma (KS)**

Since the advent of HAART, there has been a dramatic and continuing decline in the incidence of KS [20], especially in the late post-HAART period compared to the early post-HAART [19]. As in the studies of Cianflone et al. (RR: 12.32, 95% CI: 0.24–12.44) [4] and van Leeuwen et al. (RR: 0.21, 95% CI: 0.18–0.24) [20], we found a reduction in the risk for developing KS after the initiation of HAART (RR: 0.30, 95% CI: 0.28–12.33). Despite the fact that the restoration of the immune system can lead to a transient increase in KS lesions, a manifestation of immune reconstitution syndrome, HAART reduces the incidence of KS by various factors, including the reduction of HIV replication, thus improving the immune responses against HHV8 and the direct anti-angiogenic activity of some protease inhibitors. Recent studies suggest that the incidence of KS in people with HIV is now stabilized at a much lower rate, although the rate is still substantially high when compared to that of the general population [12].

**Non-Hodgkin’s Lymphoma (NHL)**

Similar to the rates of KS, we found a reduction in the risk for developing NHL after the introduction of HAART (RR = 0.52, 95% CI: 0.48–0.56). Although some studies show that the decline in the incidence is stabilizing, others show that the decline continues even when comparing the early post-HAART periods to the late post-HAART era, suggesting that in the future, the difference in risk between the general population and HIV-infected population will disappear [12,20]. The reduction in the risk of NHL is directly related to the increased CD4 count; however, for Burkitt’s lymphoma, that is not true because this type of NHL occurs when the CD4 count is relatively high (>200 cells/mm³) [24]. Even so, we found a reduction in the risk for Burkitt’s lymphoma since the introduction of HAART (RR: 0.44, 95% CI: 0.27–0.73), as well as in the risks for primary lymphoma of the central nervous system (RR: 0.24, 95% CI: 0.20–0.30) and diffuse large B-cell lymphoma (RR: 0.44, 95% CI: 0.27–0.73).
Invasive cervical cancer (ICC)

Unlike other AIDS-defining malignancies, the incidence of invasive cervical cancer does not seem to have diminished after the advent of HAART [25]. Cohort studies with individual patient data on HAART use have produced conflicting results with a reduced risk associated with HAART reported in some but not all studies [12]. We found an increased risk for developing invasive cervical cancer after the introduction of HAART (RR: 1.46, 95% CI: 1.09—1.94), similar to what was found by Gings and Gill [26] in 2006. The increased incidence for developing invasive cervical cancer, even after the advent of HAART, may have several explanations, including the fact that the female population with HIV is living longer, that antiretroviral therapy does not prevent the appearance of ICC as it was thought to previously, or even that there is an inadequate screening program for women living with HIV [27]. Thus, it is unclear how the immune reconstitution induced by HAART affects the lesions induced by HPV; more research is needed to establish a secure association [28].

When comparing the data between these studies, some limitations in the source data must be considered. In the included studies, most reports included person-years from the 5 years before the onset of AIDS, but others included only the post-AIDS period, and the duration of the post-AIDS follow-up period varied. This may explain the heterogeneity among the studies included in this systematic review. Because immune deficiency varies considerably during the natural history of HIV infection and is also affected by treatment, the degree of immune deficiency probably varied across the HIV/AIDS studies. Finally, some studies did not report data covering all cancer types. Nonetheless, there was no demonstrable publication bias.

Conclusion

Arguably, HAART contributed to the increased survival of people living with HIV by providing greater control of viral replication and increased immunity. This somewhat explains the reduction of new cases of AIDS-defining carcinomas such as KS and NHL in the post-HAART era because the incidence of these cancers decreases in the immunocompetent population.

In addition, the increased survival allowed the detection of malignant tumors, as NADCs (liver, lung and prostate) were greatly undiagnosed before the introduction of HAART because these carcinomas arising in HIV-infected individuals were uncommon in the pre-HAART era.

Moreover, other factors are associated with the lower or higher incidence of cancers following the introduction of HAART. Some are already well defined, such as the hepatotoxicity of HAART that may predispose patients to the emergence of hepatic carcinoma and immune reconstitution, which increases the number of lymphocytes infected with EBV. However, it is not completely known how these factors increase the carcinomas of the lung, prostate and cervix in the post-HAART era, and larger studies are needed to elucidate these interactions.

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Competing interests
None declared.

Ethical approval
Not required.

References


