

Incidence and mortality of non-AIDS-defining cancers among people living with HIV: A systematic review and meta-analysis

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Summary

Background Non-AIDS-defining cancers (NADCs) are now becoming a rising cause of morbidity among people living with HIV (PLHIV) in the highly active antiretroviral therapy (HAART) era. We conducted a systematic review and meta-analysis to estimate the summary risk of incidence and mortality of a wide range of NADCs among PLHIV compared with the general population.

Methods This systematic review and meta-analysis was registered in the PROSPERO (registration number CRD4202022020). We searched PubMed, EMBASE, Cochrane library, and Web of Science for relevant studies published before Jan 24, 2022. Cohort or registry linkage studies comparing the incidence or mortality of individual NADCs in PLHIV with that in the general population were included. Studies simply reporting outcomes of cancer precursor lesions or combined NADCs were excluded. We calculated pooled standardised incidence (SIRs) and standardised mortality ratios (SMRs) and their 95% confidence intervals (CIs) using random-effects models, and used robust variance estimation to account for non-independence in study-level effect sizes.

Findings We identified 92 publications arising from 46 independent studies including 7 articles out of 7 studies from developing countries. Among the 40 types of NADCs investigated, all of the 20 infection-related NADCs, cancers related with human papillomavirus infection in particular, and half of the 20 non-infection-related NADCs occurred in excess in PLHIV compared with the general population. This risk pattern was consistent in most WHO regions and in both high-income and low-and middle-income countries. The increased SIRs for various NADCs were more evident among PLHIV with advanced immunodeficiency, and was explored by HIV transmission route, and use of HAART. PLHIV had increased mortality for anal cancer (SMR 124.07, 95% CI 27.31–563.72), Hodgkin lymphoma (41.03, 2.91–577.88), liver cancer (8.36, 3.86–18.11), lung cancer (3.95, 1.52–10.26), and skin melanoma (3.95, 1.28–12.2).

Interpretation PLHIV had increased incidence and mortality for a wide spectrum of NADCs. Primary prevention and effective treatment for NADCs in this population is urgently needed.

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Research in context

Evidence before this study

Two previous meta-analyses published in 2007 and 2009 found an increased incidence for a range of non-AIDS-defining cancers (NADCs) among people living with HIV (PLHIV) in developed countries. Since the publication of the last review, a large amount of new evidence has emerged worldwide, in developing countries in particular. In addition, findings of studies on mortality for NADCs comparing PLHIV to the general population are mixed and un-synthesized.

Added value of this study

We did a comprehensive review on the incidence and mortality of NADCs among PLHIV in comparison with the general population. Based on 46 included studies, we found that PLHIV have higher incidence for 30 out of 40 types of NADCs identified, of which half were infection-related. This increased risk pattern was consistent in both high-income and low- and middle-income countries, and was more pronounced among moderately or severely immunocompromised PLHIV. We also explored variation in the incidence of NADCs by WHO region, sex, HIV transmission route, and HAART use. Regarding the mortality of nine NADCs identified, PLHIV were found to have an elevated risk of dying from anal cancer, Hodgkin lymphoma, liver cancer, lung cancer, and skin melanoma.

Implications of all the available evidence

This is a comprehensive meta-analysis of global literature on all identifiable NADCs among PLHIV, which showed elevated morbidity and mortality of most NADCs. It is suggested that there is a need for primary prevention and effective treatment for NADCs among PLHIV. More long-term clinical cohort studies controlling for confounding factors are needed to investigate the impacts of HIV-induced immunodeficiency and HAART use on the incidence risk and prognosis of NADCs. Nevertheless, more relevant evidence from developing settings is also needed.

Introduction

It is well-established that people living with HIV (PLHIV) have high risk of developing acquired immune deficiency syndrome (AIDS)-defining cancers (i.e., Kaposi's sarcoma, non-Hodgkin lymphoma, and cervical cancer).^{1,2} With the massive introduction of highly active antiretroviral therapy (HAART) worldwide, however, there has been a rise in incident non-AIDS-defining cancers (NADCs) among PLHIV in both developed and developing countries,^{3,4} and this trend is projected to persist in the future.⁴ With potent antiretroviral drugs, PLHIV are living a longer life, and the age-related diseases including different types of NADCs are becoming increasingly important health issues in this population.^{5,6} Meanwhile, NADCs are an increasingly important cause of morbidity and mortality among PLHIV worldwide. For example, a study conducted in the US reported that during 2001 to 2015, 9.2% of deaths in PLHIV were attributable to NADCs, in comparison with 5.0% of deaths attributable to AIDS-defining cancers.⁷ During the same time period, the population-attributable fractions of mortality for NADCs rose from 7.2% to 11.8%.⁷ Similar findings were also reported by cohorts studies from Turkey⁸ and China.⁹

The first meta-analysis on this topic was published in 2007 and based on seven studies,¹⁰ and the latest updated meta-analysis was published in 2009 and additionally included six studies.¹¹ Both reviews reported an elevated incidence for the majority types of NADCs among PLHIV compared with the general population, especially for cancers related to infection and smoking.^{10,11} However, the latest meta-analysis searched studies published until March 2009, which is now more than a decade old. There was a limited number of studies available for subgroup analyses to explore the impact of patients' demographic and clinical characteristics on the incidence of NADCs. Additionally, studies included in these reviews were all from developed settings.^{10,11} Results and conclusions derived from the two reviews might have limited representativeness from a global perspective, as most of PLHIV are living in developing settings. During the past ten years, a large

amount of new evidence has emerged around the world.^{12–53} Thus, there is a need for an updated meta-analysis to provide a more comprehensive review of the morbidity of NADCs.

Several recent studies found that PLHIV have relatively poorer prognosis and survival for some NADCs in comparison with the general population.^{54–58} For example, studies conducted in the US reported elevated standardized mortality ratios (SMRs) for some common NADCs, such as cancers of the liver, lung, and colon and rectum in PLHIV.^{56–58} Understanding the risk of death attributable to various NADCs could inform disease management and treatment among PLHIV. To the best of our knowledge, however, so far there has been a lack of summary and meta-analysed data on the mortality risk of NADCs among PLHIV.

To fill these knowledge gaps, we aimed to extend previous investigations on the incidence of NADCs among PLHIV compared with the general population through including all available literature and performing detailed subgroup analyses. Besides, we aimed to provide the first summarized estimates regarding the mortality of NADCs among PLHIV in comparison with the general population.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was registered in the PROSPERO International Prospective Register of systematic reviews (registration number CRD42020222020). We followed the PRISMA guidelines,⁵⁹ and completed checklist could be found in the appendix. We searched PubMed, EMBASE, Cochrane library, and Web of Science for studies published as of 24 Jan 2022. References of relevant reviews and full-text articles and included literature were screened for additional studies that may have been missed. We used a combination of Medical Subject Headings and key words related to HIV, cancer, incidence, and survival and adapted them to different databases. The full search strategy for each database is provided in the appendix.

We included studies if they were a cohort study or registry linkage study of PLHIV, recruited predominantly adults, compared the incidence or mortality of NADCs in PLHIV and that in the general population; reported or had sufficient data (i.e., standardised incidence ratios [SIRs] or SMRs and 95% confidence intervals [CIs]) to compute the observed and expected cases of NADCs. Multiple publications deriving from a single cohort study were included, and we used meta-analysis with robust variance estimation (RVE) in conjunction with three-level meta-analysis to deal with non-independent effect sizes.⁶⁰ We excluded studies that only treated all NADCs combined as a single outcome, only reported outcomes for cancer precursor lesions, and did not distinguish PLHIV from other populations.

Two pairs of investigators (TY, YH, XZ, and LY) independently performed the search and assessed each study for inclusion. The titles and abstracts of retrieved studies were first assessed for eligibility by two authors. Potentially eligible studies were retained for full text check, and inclusion was determined by reading the full text of these studies. Disagreements were resolved through discussion with a senior scientist (HZ).

Statistical analysis

Three investigators (XZ, LY, and YH) independently extracted study-level characteristics for each study, including study type, cohort name, first author, publication year, publication type, study country, study setting, follow-up or registry-linkage duration, and sample size. Study countries were grouped by WHO region and the latest World Bank income level.⁶¹ We extracted observed and expected number of incident cancer cases or death cases by anatomical sites of cancer for calculation of $\log_e(\text{SIR})$ or $\log_e(\text{SMR})$ and corresponding standard errors. When the number of expected cases was not reported, we calculated it by dividing the number of observed cases by the reported SIR or SMR. In some instances where neither the number of observed nor expected cases was reported, they were calculated based on reported SIRs or SMRs and their upper 95% confidence intervals (CIs) by the following equation⁶²:

$$\begin{aligned} \log_e(\text{upper } 95\% \text{ CI}) \\ &= \log_e(\text{SIR or SMR}) \\ &\quad + 1.96 / \sqrt{\text{the observed number of cases}} \end{aligned}$$

We also extracted outcome data by subgroups as reported by authors. Another investigator (TY) finally checked the correctness of all the extracted or calculated information, and disagreements were resolved through discussion among the four investigators. When we were unable to calculate required data, we contacted the corresponding author of the study to request the information. Extracted sites of cancer were recoded, where necessary, in accordance with the International Classification of Diseases, 10th Revision.⁶³ We further grouped NADCs by infection-related cancers and cancers remotely relevant or irrelevant to infection.⁶⁴

The methodological quality of included studies was assessed by a checklist consisting of 14 questions adapted from the US National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-sectional studies (appendix).⁶⁵ One point was assigned to each question if the study met that criterion, thus the total score ranged from 0 to 14. We summarized the overall quality of included studies in terms of the median and interquartile range (IQR) of the total scores. Two pairs of investigators (TY, YH, XZ, and LY) independently assessed the study quality, and any

disagreement was resolved by discussion with a senior author (HZ).

When the outcome of a specific NADC was reported by more than one independent studies, the pooled effect sizes (i.e., SIRs or SMRs) together with their 95% CIs were calculated using random-effects meta-analysis, since we assumed a high potential for heterogeneity across included studies.⁶⁶ Conventional meta-analysis assumes that individual effect sizes are independent. However, violation of this assumption is a common phenomenon, which could occur when multiple publications are derived from a same cohort study or database, or when one study reports multiple effect estimates for a same outcome among overlapped populations (e.g., three separate effect sizes across three periods of time). Selecting one effect size per independent population either by random or according to a predefined rule is a common approach to avoid such dependence.⁶⁰ But it is not an efficient approach in that not all available information is used to address the research question.⁶⁰ To overcome this problem, we primarily used RVE to handle non-independent effect sizes in our meta-analysis. A major advantage of RVE is that it does not require information on the exact form of dependency, which is typically unknown.^{60,67} Conversely, one limitation of RVE is that when the number of studies is small or moderate, CIs calculated from RVE could have very large Type I error.^{67,68} In order to minimize this bias, we implemented small sample adjustment proposed by Tipton for all RVE analyses.⁶⁸ Furthermore, for outcomes with a very small number of studies (less than five), if the dependence was caused by multiple publications embedded in a same cohort, we only retained the latest publication; if the dependence was caused by one study reporting multiple effect sizes for a same outcome among overlapped populations, we performed a three-level meta-analysis.⁶⁰

We did subgroup analyses across different HIV risk groups (i.e., men who have sex with men [MSM], injection drug users [IDU], and heterosexual individuals), which might have different risk pattern but remain unsynthesized by previous reviews. As surrogates for immunodeficiency levels, we performed subgroup analysis for studies that compared PLHIV without an AIDS diagnosis and PLHIV with an AIDS diagnosis, and that compared cancer risks in time periods relative to an individual's onset of AIDS. AIDS is the most advanced stage of HIV infection, represented by having a CD4 cells being below 200 cells/mm³, or the presence of an AIDS-defining condition (e.g., opportunistic infection).² The AIDS case definition used in different studies might vary, though none of the included studies reported the concrete definition used. We also performed subgroup analyses by income of country,⁶¹ WHO region, sex, individual HAART use, and time periods relative to HAART era, which were categorized into four groups in total, according to included studies reporting this subgroup

outcome^{12-14,17,18,23,24,26,32-34,40,69-79} (i.e., 1980-1989: no/limited antiretroviral therapy [ART]; 1990-1995: mono and dual ART; 1996-2001: early HAART era; 2002-2013: later HAART era).

We used I^2 statistic to assess the level of heterogeneity across included studies, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. To explore potential source of heterogeneity across studies, we additionally performed subgroup analyses by study design (registry linkage study vs cohort study), study setting (population-based vs hospital based), and sample size (< medium value vs \geq medium value). We did not formally test publication bias by using funnel plot or the Egger's test, since these techniques are not applicable in the setting of using RVE.⁸⁰ For sensitivity analysis, in the case of multiple publications derived from a same cohort, we retained the latest publication and only accounted for the dependence resulting from one study reporting multiple effect sizes for each outcome by using three-level meta-analysis. We additionally performed sensitivity analysis excluding studies of low quality (i.e., total quality assessment score below the first quartile).

All data analyses were done using R version 4.1.2 with packages robumeta, metafor, and forestplot.

Role of the funding source

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Results

We identified 92 publications arising from 46 independent studies (Figure 1). Forty-two studies (85 publications^{12-53,64,69-79,81-111}) only reported the outcome of cancer-specific SIRs among PLHIV, four studies (6 publications^{54-58,112}) only reported the outcome of SMRs,

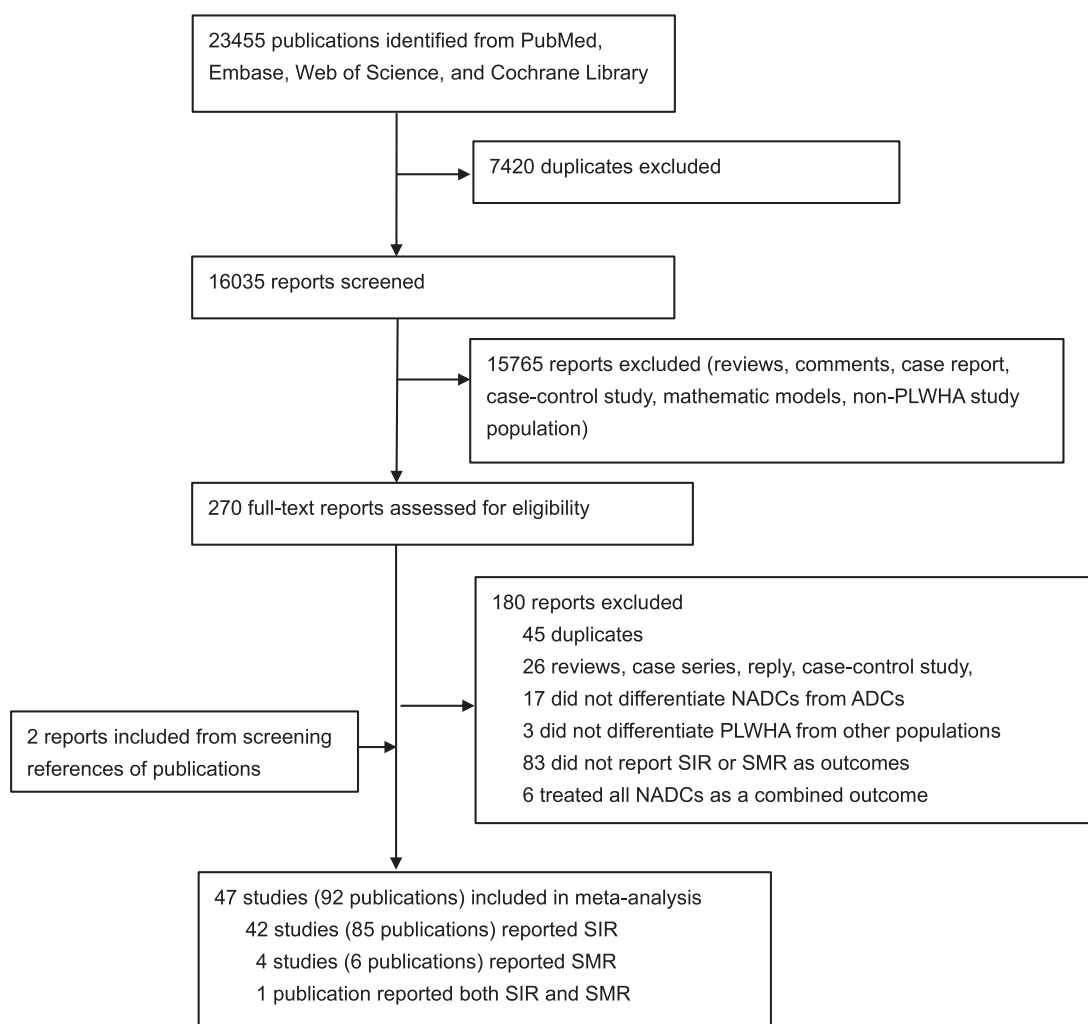


Figure 1. Flow chart of selecting studies for inclusion.

Abbreviations: PLHIV, people living with HIV; NADCs, non-AIDS-defining cancers; ADCs, AIDS-defining cancers; SIR, standardised incidence ratio; SMR, standardized mortality ratio.

and one study reported both the outcome of SIRs and SMRs.

Details of included publications are in the supplementary Table S1. Overall, included publications were published between 1992 and 2022, with commencing years of follow-up or linkage duration ranging from 1978 to 2010. The number of PLHIV included in each publication ranged from 196 to 615150. Included studies predominately come from high-income countries (85%, 39/46), and most of them were conducted in Americas (41%, 19/46) and Europe (39%, 18/46). The individual study estimates of cancer-specific SIRs or SMRs are shown in the supplementary Tables S2 and S3. The methodological quality of included studies was largely acceptable, in that most studies scored eight out of the 14 quality assessment items (median score [IQR]: 8 [7-9]). Detailed quality assessment results for

each included study can be found in supplementary Table S4.

We meta-analysed the SIRs of a total of 40 types of NADCs among PLHIV (Figure 2). Nearly all types of the 20 infection-related NADCs occurred at increased rates among PLHIV in comparison with the general population. The highest summary SIRs were observed in HPV-related cancers of the anogenital sites, including cancers of the anus and anal canal (SIR 28.33, 95% CI 20.30-38.96, $I^2 = 93\%$), vulva and vagina (14.13, 7.58-26.36, $I^2 = 71\%$), and penis (7.60, 3.68-15.70, $I^2 = 81\%$). Cancers with markedly increased rates also included Hodgkin lymphoma (10.83, 8.88-13.17, $I^2 = 81\%$), eye and adnexa cancer (8.97, 2.95-27.28, $I^2 = 83\%$), and liver cancer (5.64, 4.42-7.19, $I^2 = 83\%$), which are related with Epstein-Barr virus (EBV), human papillomavirus (HPV), and hepatitis B/C virus (HBV/HCV)

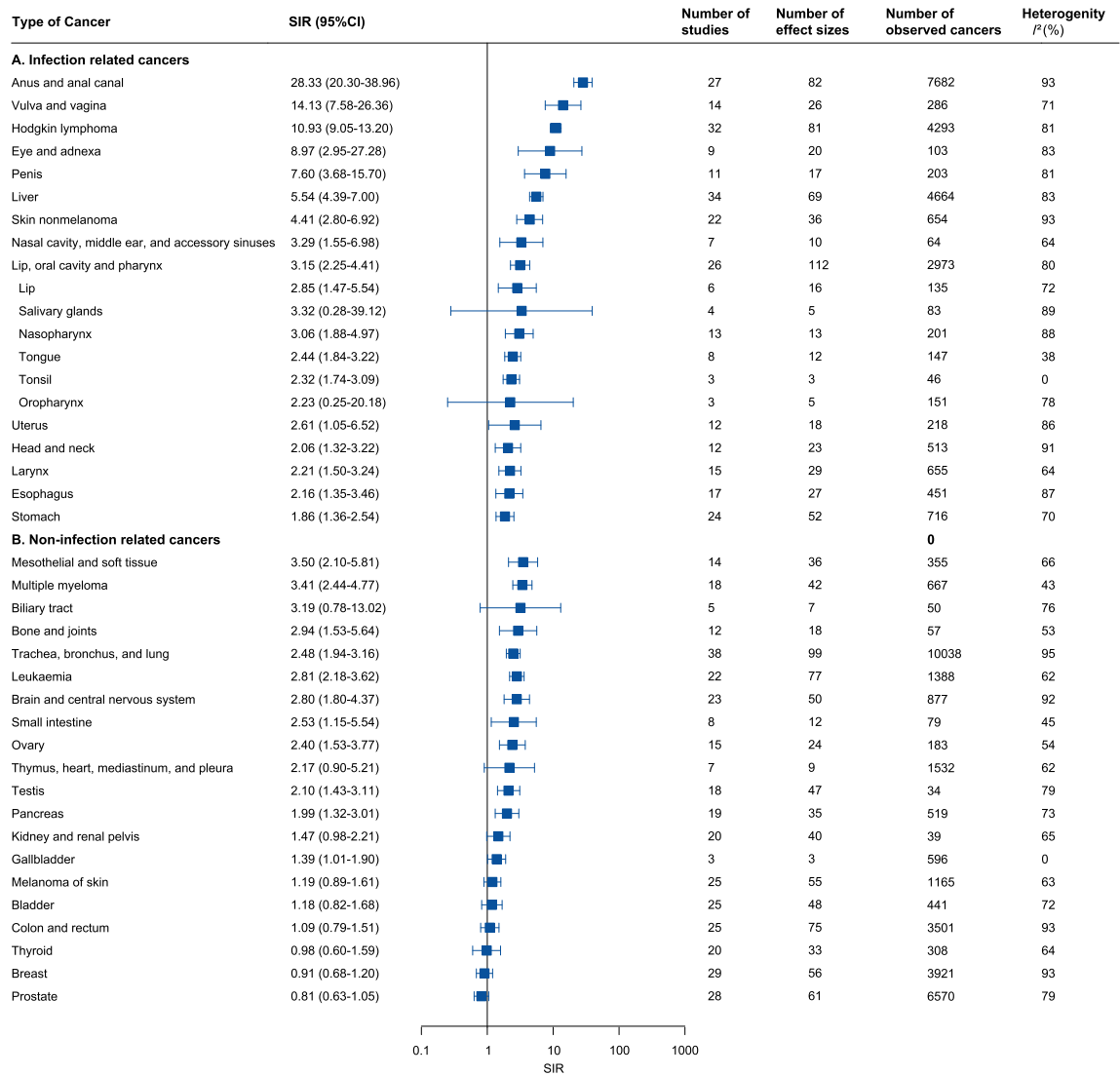


Figure 2. Meta-analysis of standardised incidence ratio for non-AIDS-defining cancers.

Abbreviations: SIR, standardised incidence ratio; CI, confidence interval.

In all the forest plots, the number of effect sizes refers to the number of single outcome estimates included in the meta-analysis, some of them were non-independent because they derived from one same study cohort or cancer registry. The number of studies refers to the number of independent cohort studies or registry linkage studies.

infection, respectively. A half of the 20 non-infection-related NADCs occurred at increased rates in PLHIV, including multiple myeloma, leukaemia, and cancers of mesothelial and soft tissue, bone and joints, lung, brain, small intestine, ovary, testis, and pancreas, with the pooled point estimates of SIRs ranging from 2.0 to 3.5. It is worth noting that PLHIV seem to have a lower risk of developing cancers of breast and prostate compared with the general population, although this difference was not statistically significant (95% CIs overlap).

The increased SIRs for NADCs observed in main meta-analyses were largely consistent in subgroup analyses by the income level of country (Figure 3). Relatively

higher SIRs in high-come countries were also observed for Hodgkin lymphoma, cancers of HPV-related anogenital sites, and liver cancer. Similar risk pattern was also observed in the subgroup analysis by WHO regions (supplementary Figure S1). Notably, the SIR for liver cancer was significantly lower in Africa (0.81, 0.36-1.80, I² = 0%) compared with that in other WHO regions (95% CIs did not overlap), and the highest SIR was observed in Europe (7.06, 5.04-9.87, I² = 90%), though there were only two existing studies from Africa.

In the subgroup analyses for SIRs by HIV risk groups (Figure 4), IDU had higher SIRs for liver cancer and lung cancer, while MSM had the highest SIR for

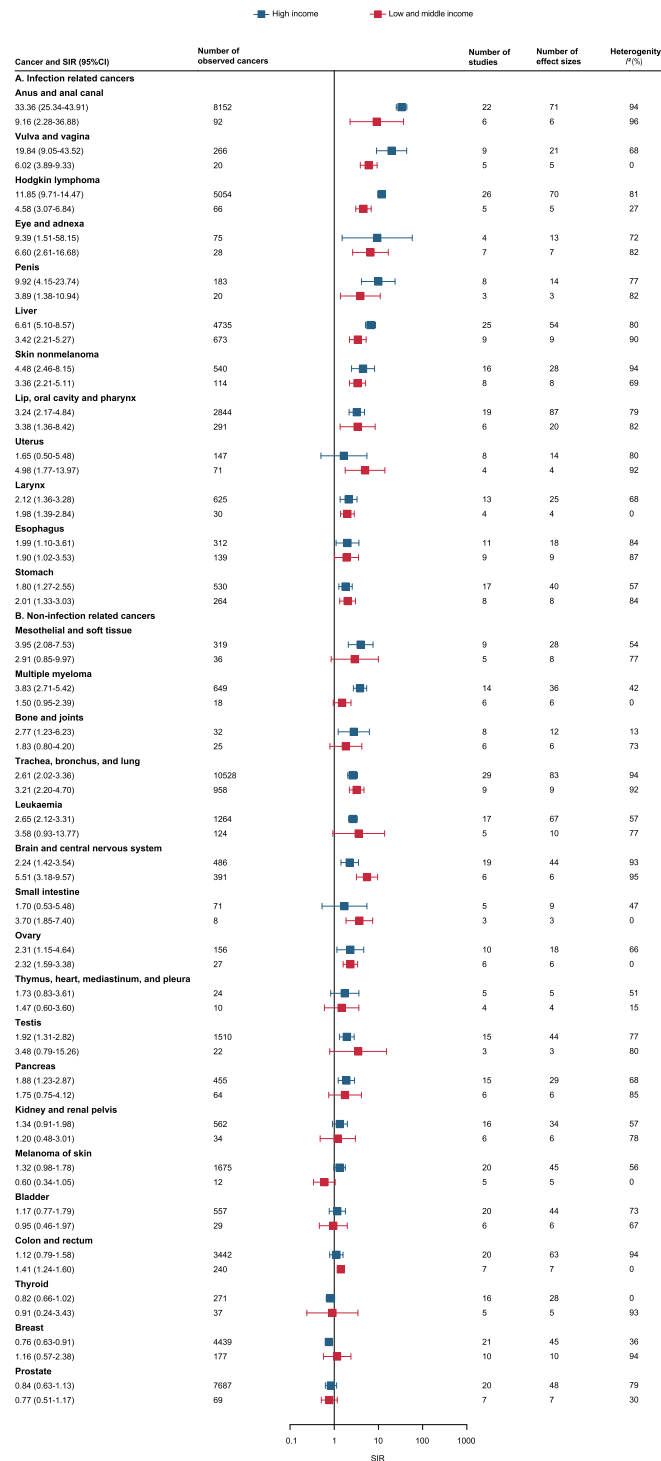


Figure 3. Subgroup analyses for SIRs by income levels of countries.
Abbreviations: SIR, standardised incidence ratio; CI, confidence interval.

anal cancer, in comparison with other groups. Conversely, MSM had lower SIRs for cancers of lip, oral cavity, and pharynx compared with heterosexual individuals. In the subgroup analyses for SIRs by sex

(supplementary Figure S2). The SIRs for cancers of the lip, oral cavity and pharynx, esophagus, stomach, multiple myeloma, lung, brain, kidney, and bladder, tended to be higher among women than among men. In

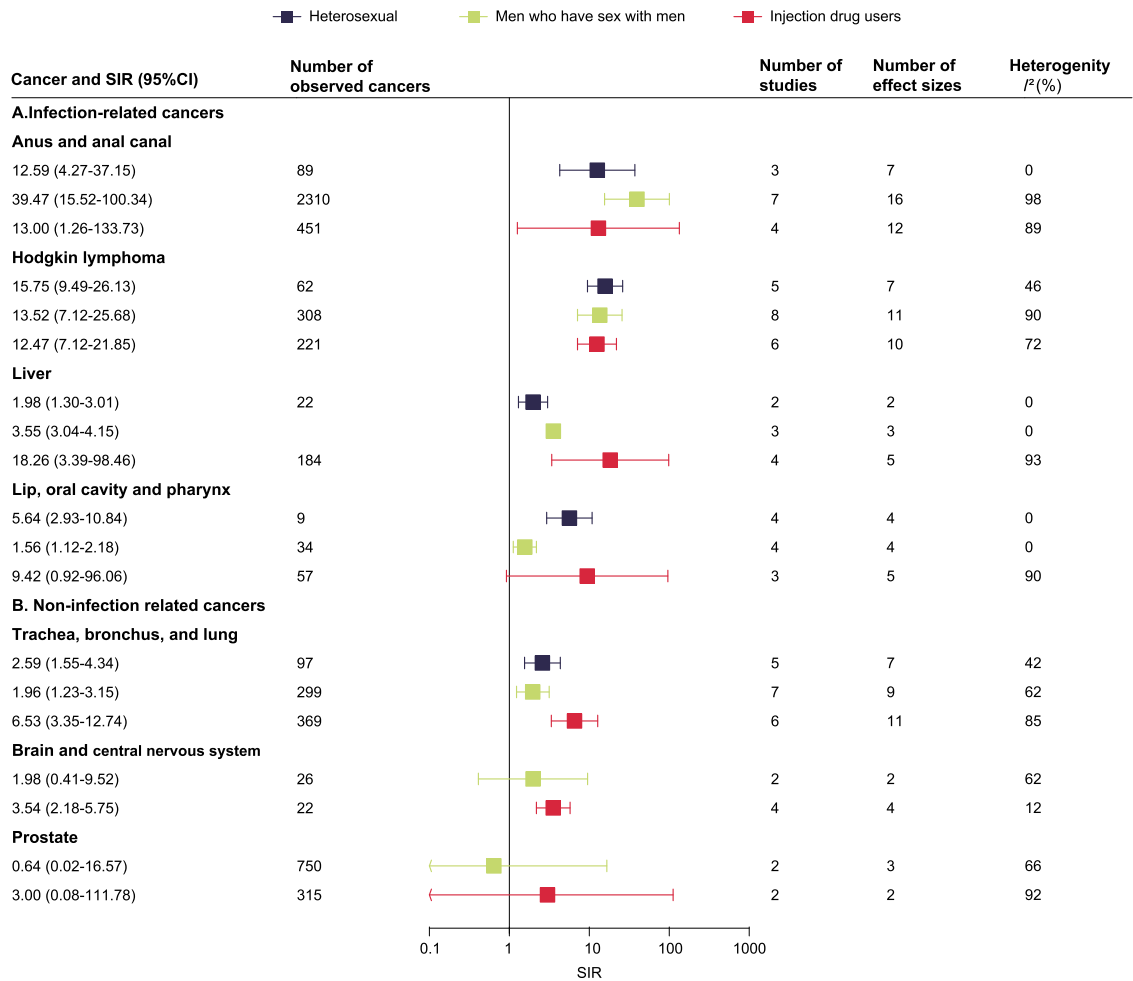


Figure 4. Subgroup meta-analysis for SIR by HIV transmission group.
Abbreviations: SIR, standardised incidence ratio; CI, confidence interval.

contrast, the SIRs for anal cancer and breast cancer appeared to be higher among men than among women.

In the subgroup analyses for SIRs by the degree of immunodeficiency (supplementary Figure S3 and S4), PLHIV with AIDS had relatively higher SIRs for all infection-related NADCs and lung cancer, leukaemia, and pancreatic cancer in comparison with those without AIDS. Similarly, in the subgroup analysis by AIDS relative period, patients at AIDS period had the highest SIRs compared with patients at other periods for nearly all types of NADCs, with the exception for colorectal cancer. Nevertheless, the numbers of studies available for the two subgroup analyses were small with limited statistical power.

Few studies were available for the subgroup analyses by the individual use of HAART. PLHIV treated with HAART tend to have higher SIRs for Hodgkin lymphoma compared with those not on HAART (supplementary Figure S5). At a population level (supplementary Figure S6), the SIRs for cancers of

anus and anal canal, vulva and vagina, liver, and Hodgkin lymphoma tended to rise in the HAART era compared to the pre-HAART era, whereas the opposite trend was observed for cancers of uterus, brain and central nerves system, and leukaemia.

We meta-analysed the SMRs of a total of nine types of NADCs in PLHIV (Figure 5). Notably, PLHIV with anal cancer had a substantially higher risk of mortality in comparison with the general population (124.07, 27.31–563.72, I² = 92%). Additionally, elevated meta-SMRs in PLHIV compared with the general population were observed for Hodgkin lymphoma (41.03, 2.91–577.88, I² = 98%), liver cancer 8.36 (3.86–18.11, I² = 76%), trachea, bronchus, and lung cancer (3.95, 1.52–10.26, I² = 87%), and melanoma of skin (3.95, 1.28–12.2, I² = 75%). We were unable to perform further subgroup analyses for SMRs because of limited number of studies available.

We observed moderate to high between-study heterogeneity for almost all main meta-analyses. In subgroup

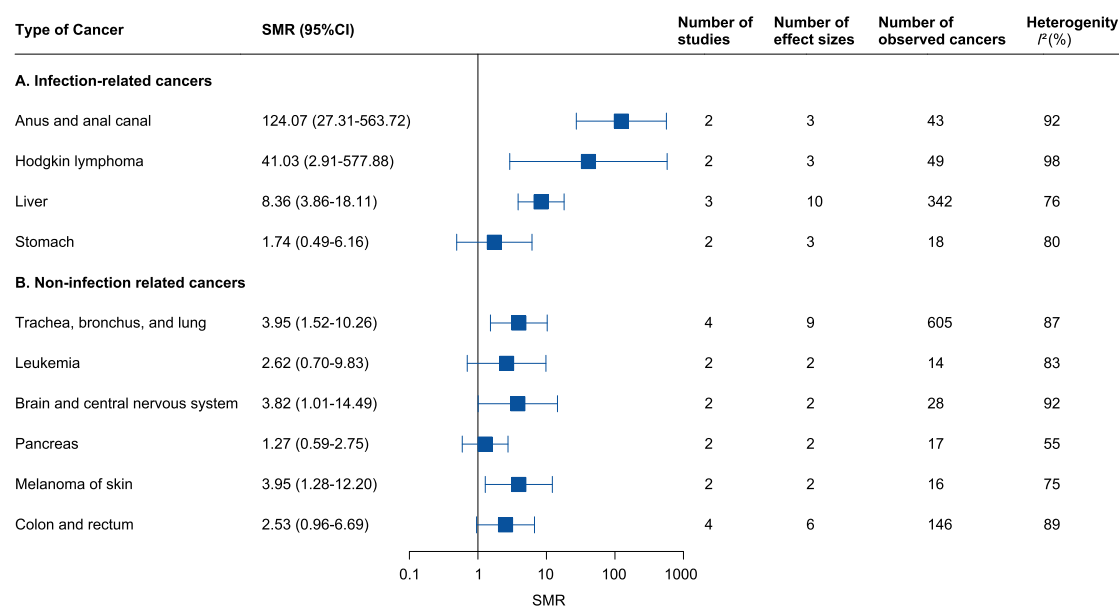


Figure 5. Meta-analysis of standardised mortality ratio for non-AIDS-defining cancers.

Abbreviations: SMR, standardised mortality ratio; CI, confidence interval.

analyses, the high level of heterogeneity was substantially reduced for most cancers in studies conducted in low-income countries, cohort studies, and studies with hospital-based setting (Figure 3, Supplementary Table 5–7). In sensitivity analyses retaining one effect size from each independent cohort study for each type of NADCs (supplementary Figures S7 and S8), the main results of the pooled SIRs and SMRs along with their corresponding 95% CIs remained robust. This is also the case for the sensitivity analyses excluding studies of low quality (Supplementary Table S8).

Discussion

In this meta-analysis, we found that PLHIV have an increased risk of developing nearly all types of the 20 infection-related NADCs and half of the 20 non-infection-related NADCs compared to the general population. This increased risk pattern was consistently observed in a range of subgroup analyses by country income levels, WHO regions, sex, and HIV risk groups, and tend to be more predominant among those with AIDS. PLHIV are more likely to die from anal cancer, Hodgkin lymphoma, liver cancer, lung cancer, and skin melanoma in comparison with the general population.

We found that NADCs with an infectious etiology occur at greater rates among PLHIV than in the general population, represented by cancers related with infection with HPV (cancers of anogenital sites, eye and adnexa, head and neck), EBV (Hodgkin lymphoma and nasopharyngeal cancer), and HBV/HCV (liver cancer). This is in line with findings from two previous meta-analyses,^{10,11} as well as individual studies with other

designs using HIV-negative individuals as the reference population.^{113,114} The elevated incidence of infection-related NADCs might be largely due to HIV-induced immunodeficiency and resultant reduced ability to fight against the infection and proliferation of oncogenic pathogens in PLHIV.¹¹ Additionally, some behaviors prevalent among PLHIV that could increase the risk of co-infection with oncogenic viruses might also play a part.

The highest SIR was observed for cancers of the anogenital sites, particularly anal cancer, most of which evolve from HPV-induced preneoplastic lesions. These might be attributable to the high incidence rate and low clearance rate of HPV in PLHIV.⁹⁰ A systematic review and meta-analysis found that the incidences of overall HPV infection and high-risk HPV infection are almost doubled among PLHIV compared with HIV-negative individuals, whereas the rate of HPV clearance was halved.¹¹⁵ Besides, both HPV and HIV are mainly transmitted by unprotected sexual contact. This means that people infected with HIV due to persistent and frequent risky sexual behaviors also have a higher likelihood of exposure to HPV, thereby higher risk of developing HPV-related cancers of anogenital sites. This is especially the case for MSM, who tend to be more sexually active compared with heterosexual individuals as indicated by earlier sexual debut, multiple sexual partners, and longer lifetime periods of acquiring new partners.¹¹⁶ This could explain the result of our subgroup analysis that MSM had the highest SIRs for anal cancer compared with other HIV risk groups. Similar findings were reported from other sources.^{117,118} The high-coinfection rate is exacerbated by the low awareness of anal

cancer screening in MSM and PLHIV, as well as the lack of relevant anal cancer screening programs.^{119–121}

Similarly, the elevated risk of liver cancer among PLHIV could be explained by high rates of co-infection with HCV or HBV attributable to risk behaviors common in PLHIV. Specifically, HCV, HBV, and HIV all could be transmitted through sexual contact, sharing drug-injection equipment, and transfusion of blood products, contributing to a higher co-infection rate and a higher risk of developing liver cancer.^{122,123} A global systematic review and meta-analysis reported that the prevalence of HCV infection was slightly elevated in HIV-negative MSM (prevalence ratio 1.58, 95%CI 1.41–2.01), but notably elevated in MSM with HIV (6.22, 5.14–7.29), in comparison with the general population.¹²⁴ Notably, the pooled HCV prevalence was substantially higher in MSM currently injected drugs (45.6%, 21.6–70.7) than those who never injected drugs.¹²⁴ Similar finding was reported by another meta-analysis that the burden of HBV co-infection among PLHIV was the highest among IDU.¹²⁵ This is in line with our subgroup analysis that the elevated SIRs for liver cancer were the highest in IDU, followed by MSM.

We found increased SIRs for a range of NADCs with weak link with infection among PLHIV. This is largely in line with findings from previous reviews.^{11,126} A higher proportion of smokers in PLHIV than that in the general population potentially contributed to a higher incidence of cancers induced by smoking (e.g., lung cancer).⁹² A meta-analysis conducted in 2016 reported that the prevalence of current smokers in PLHIV in the US was around 54%, nearly doubling the figure in US adults (20–23%). Another meta-analysis also reported high prevalence of behavior-related cancer risk factors including smoking (41%) and alcohol consumption (30%) among PLHIV in China.¹²⁷

Additionally, HIV-induced immunosuppression itself might also be a risk factor for some non-infection-related cancers. In fact, studies found that HIV infection itself could induce oncogenesis by disturbing normal cell cycle, altering oncogene regulation, and increasing oxidative stress.^{69,77} Lastly, it was possible that AIDS-related cancers could be misdiagnosed as some non-infection-related NADCs, especially in the absence of histological confirmation. For instance, Kaposi's sarcoma could be misdiagnosed with cancers of mesothelial and soft tissue, and non-Hodgkin lymphoma could be confused with brain cancer and leukemia.^{70,92,95}

We found that the pattern of increased SIRs was largely consistent across countries of different income-levels and WHO regions. This might reflect the success in the rapid expansion of HAART program on a global scale, therefore the prolonged life expectancy of PLHIV in both high-income and low-and middle-income countries allows the development and onset of various NADCs. The relatively higher SIRs for cancers of the anogenital sites and Hodgkin lymphoma in developed

countries than in less developed countries might be due to the higher proportion of older PLHIV in high-income countries than in developing countries,¹²⁸ because age is a key risk factor to cancer development.¹²⁹ Another possible explanation could be attributable to better diagnostic methods and higher frequency of cancer screening in developed countries compared with developing countries. But these reasons cannot explain the absence of intra-subgroup differences for other types of NADCs. Different countries have different population age structures and cancer incidence rates in the general population, making the comparison of SIRs difficult.

In our subgroup analysis by HIV risk groups, MSM had lower SIRs for cancers of lip, oral cavity and pharynx compared with heterosexual individuals. Interestingly, one study conducted in England reported that homosexual women have significantly increased risk for oropharyngeal cancer compared with heterosexual women, which was not observed when comparing MSM with heterosexual men.¹¹⁷ The collective evidence indicates that having a female sex partner might be a risk factor for oropharyngeal cancer. A possible explanation might be the higher probability of HPV transmission via oral sex performed on the vulva or vagina than oral sex performed on the penis as being reported by previous studies.^{130,131}

Consistent with a previous meta-analysis,¹¹ we identified a relatively higher SIRs among HIV-infected women than that among HIV-infected men for a range of cancers (e.g., cancers of head and neck, larynx, stomach, lung, bladder and kidney). The underlying reason for this sex difference is less clear and warrants further investigation from direct comparison in the form of incidence rate ratios adjusted for age and period.¹³² We also found a lower incidence of breast cancer among HIV-infected women compared with the general population. Previous studies proposed that it might be because HIV could bind to the chemokine receptor CXCR4 expressed by breast cancer cells and result in apoptosis.^{19,44} But the reduced incidence in breast cancer was not observed among male HIV-infected patients, though the finding was only based on three studies. Similarly, we observed a reduced risk of prostate cancer among male PLHIV compared with the general population. This could be due to a reduction in androgen levels caused by HIV infection.^{17,18} Alternatively, reduced risk for cancers of both breast and prostate might reflect the lower rate of screening for the two types of cancer in PLHIV in comparison with the general population.¹⁷

Consistent with a previous meta-analysis,¹¹ we found that the increased SIRs for various cancers tend to be more pronounced among patients with AIDS versus those with HIV only. We additionally compared the SIRs at different periods relative to AIDS stage and similar results were found. These might reflect that higher immunosuppression level might enhance the risk of developing NADCs. However, AIDS stage is only an

indirect proxy of the degree of HIV-induced immunosuppression, and results of our comparisons are highly likely to be confounded by age. A better option would be investigating the relationship between CD4 cell counts and the risks of various NADCs among PLHIV.

PLHIV treated with HAART were found to have relatively higher SIRs for Hodgkin lymphoma than those not using HAART. Similarly, we found a higher SIR for Hodgkin lymphoma in the HAART era, especially in early HAART era, compared with that in the pre-HAART era. Results from a previous meta-analysis also found elevated SIRs for kidney cancer and breast cancer in the HAART era compared to the pre-HAART era.¹¹ However, none of these differences were statistically significant. Conversely, previous studies using adjusted incidence rates of Hodgkin lymphoma and comparing the risk internally among PLHIV between HAART users and nonusers, or between pre-HAART era and HAART era, did not find these increases.^{133,134} In fact, HAART use can be heavily confounded by CD4 cell count and other confounding factors, which were not controlled by included studies. Moreover, it has been argued that it could be problematic to directly compare SIRs for Hodgkin lymphoma over time. Because the dominant subtype of Hodgkin lymphoma in the general population (nodular sclerositis) has a unique bimodal age-specific pattern compared with the dominant subtypes in PLHIV (mixed cellularity and lymphocyte-depleted forms).¹³³ Specifically, in the general population, age-specific incidence of Hodgkin lymphoma decreases between ages 30 to 60 years, whereas the mean age of PLHIV have increased from 34.2 years in pre-HAART era to just over 40 in the HAART era.¹³³ The decreased background incidence results in the increased SIRs for Hodgkin lymphoma in HAART era.¹³³ Similarly, although we observed higher SIRs in the HAART era compared with that in pre-HAART era for cancers of the anus and anal canal, vulva and liver, we are unable to infer the potential toxicity of HAART for the development of these cancers. Because there are shifts in age distribution among PLHIV over time with fewer elderly PLHIV pre-HAART era, which means that SIRs were standardised to different age groups and thereby incomparable.¹³³

We found PLHIV were more likely to die from five (i.e., anal cancer, Hodgkin lymphoma, liver cancer, lung cancer, and skin melanoma) out of the nine investigated NADCs compared with the general population. This might be a result of relatively higher incidence of these NADCs among PLHIV than that in the general population. Another explanation could be due to more advanced cancer stage at diagnosis in PLHIV.¹⁹ This could result from the delay in seeking health care as PLHIV may be afraid of facing HIV-related stigma from health care providers.¹³⁵ Additionally, PLHIV receiving chemotherapy could suffer from HIV-induced immunodeficiency and drug toxicities from both anti-cancer

agents and HAART, leading to higher risk of infectious complications and poorer survival.¹⁹

This study has several strengths. Compared with previous meta-analyses, our findings are of greater breadth and depth. The number of studies included in this meta-analysis more than double those of prior studies meta-analyzing SIRs of cancers in PLHIV. This allows us to investigate a broader range of cancers and conduct more detailed subgroup meta-analyses to demonstrate the consistency of elevated risks. Studies included in our meta-analysis are from countries of broader geographic and economic diversities, increasing the generalizability and representativeness of our results. We also conducted subgroup analysis for SIRs stratified by WHO regions and country income levels, thereby providing a comprehensive overview on a global scale. Additionally, we for the first time provided synthesized evidence for SMRs of various NADCs among PLHIV. Lastly, by using RVE and multilevel meta-analysis, we were in a position to both properly handle non-independence and make use of all available evidence.

Findings from this study are subject to several limitations. First, studies included in our meta-analyses are predominately registry linkage studies. The completeness of cancer, HIV, and death registration as well as the accuracy of linkage could sway the accurateness of our results. Second, we specifically included only studies using SIRs or SMRs to measure the risk of NADCs. This prevented us from providing a more accurate and direct comparison across different subgroups because risk ratios might be standardised to different background populations. Evidence from studies using other measures of estimate (e.g., rates ratio, hazards ratio) adjusted for important confounders is also informative, and could be even more relevant in terms of investigating important factors (e.g., CD4 cell count, HAART use) impacting the risk of NADCs in PLHIV. Additionally, there might exist misclassification between some NADCs and AIDS-defining cancers in included studies. Fourth, due to inadequate information provided by included studies, we were unable to account for other cancer risk factors, cancer screening, and cancer histological subtypes that might confound our findings. Due to the same reason, we were unable to investigate the relationship between more direct indicators of HIV-induced immunosuppression, such as CD4 cell count and HIV viral load, and incidence or mortality of NADCs. Similarly, the impact of using different HAART regimens on cancer incidence and mortality remain unexplored. This is especially relevant given that new antiretroviral agents for PLHIV are continuously made available. Fifth, some of our findings ought to be considered as preliminary in that they were based on a small number of studies. Besides, results of our subgroup analysis were impacted by unadjusted confounding factors, especially age, across groups. Sixth, we only searched for peer-reviewed journal articles

published in English, and did not search for grey literature. This might aggravate the issue of publication bias in our results, which was unable to be assessed in our RVE meta-analyses. Lastly, findings from our meta-analyses are subject to moderate to high between-study heterogeneity and potential publication bias.

More well-designed clinical cohort studies of PLHIV are needed to better clarify the role of HIV-induced immunodeficiency and HAART on the risk of developing and dying from various NADCs.⁹⁶ Such cohort studies should ideally have long-term follow up and detailed individual record of known cancer risk factors, biomarkers of immunodeficiency, and treatment regimens. Further meta-analyses could be conducted to synthesize other types of estimates measuring the association between HAART use or the degree of HIV-induced immunodeficiency indicated by CD4 cell counts and the risk of NADCs among PLHIV. Similarly, more studies directly comparing the risk of NADCs across relevant subgroups (e.g., age, sex, HIV risk groups) adjusted for confounders are needed. Besides, only 16% of identified studies were from low-and middle-income countries, and few studies were from Africa and Southeast Asia where HIV/AIDS conflicts high disease burdens. More evidence from these resource-limited regions is needed.

Our findings suggest that aside from timely initiation of HAART, there is also a need for heightened primary, secondary, and tertiary prevention efforts for NADCs among PLHIV. Special attention should be paid to NADCs occurring at high rate among high-risk populations (e.g., anal cancer in MSM and liver cancer in injection drug users), with a focus on monitoring and modifying risk behaviors that could increase the risk of developing NADCs. Specific strategies to prevent leading NADCs could include vaccination against oncogenic viruses (e.g., HPV and HBV), treatment of coinfections, health education to modify risky lifestyles and behaviors, screening for cancer precursors, and enhanced monitoring and management of PLHIV with cancer.^{26,71} Special efforts to improve cancer screening and treatment service should be invested for PLHIV facing stigma (e.g., MSM, injection drug users) and those having other barriers, particularly financial barriers, to access to cancer care. Although PLHIV may have free access to HIV treatment in many countries, they rarely enjoy quality cancer screening and treatment. Notably, few of these plausible cancer prevention strategies (e.g., early screening, vaccination) are at scale in resource-limited countries with high burden of HIV. Mathematical modelling studies could be developed to evaluate the cost-benefit and cost-effectiveness of these cancer prevention programs among PLHIV or specific sub-populations in different countries.²⁴

Contributors

T.Y. and H.Z. conceived the study and designed the protocol. T.Y., Y.H., X.Z., and L.Y. conducted study

selection, data extraction, and statistical analysis. T.Y. drafted the manuscript. G.C., J.W., H.Q., and H.Z. critically revised the manuscript. T.Y., Y.H., X.Z., and L.Y. contributed equally to the manuscript.

Data sharing statement

All data generated or analysed during this study are included in the supplementary files.

Declaration of interests

We declare no competing interests. HZ was supported by the Natural Science Foundation of China Excellent Young Scientists Fund [82022064], Natural Science Foundation of China International/Regional Research Collaboration Project [72061137001], the National Science and Technology Major Project of China [2018ZX10721102], the Sanming Project of Medicine in Shenzhen [SZSM201811071], the High Level Project of Medicine in Longhua, Shenzhen [HLPM201907020105], the Shenzhen Science and Technology Innovation Commission Basic Research Program [JCY]20190807155409373], and the Special Support Plan for High-Level Talents of Guangdong Province [2019TQ05Y230]. LL was supported by the Guangzhou Basic Research Program on People's Livelihood Science and Technology [202002020005], the National Natural Science Foundation of China [82072265].

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101613.

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