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The effect of non-AIDS-defining cancers on people living with HIV

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Abstract

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Contributors

EYC and KS developed the idea for this Review. EYC, KS, AC, DK, VF, NN, and AM drafted the Review and KS, AC, and DK prepared the tables. EYC, KS, AC, and DK completed the scoping and ancillary reviews. All authors contributed to interpretation of the findings, editing the article, and approved the final submitted version.

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Non-AIDS-defining cancers are a growing source of morbidity for people with HIV globally. Although people living with HIV have a disproportionately increased risk of developing virally mediated cancers, cancer burden for common non-AIDS-defining cancers that are not virally associated and are linked to ageing, such as prostate cancer, is becoming higher than for virally mediated cancers. Ageing, behavioural, and HIV-specific factors drive the incidence and affect the outcomes of non-AIDS-defining cancers, presenting different challenges for addressing global morbidity and mortality from non-AIDS-defining cancer. Although large population-based studies have shown that people living with HIV with non-AIDS-defining cancers have poorer cancer outcomes than do people without HIV, current guidelines emphasise that people living with HIV with non-AIDS-defining cancers should receive standard, guideline-based treatment, and infectious disease and oncology providers should work closely to address potential drug interactions between antiretroviral therapy and antineoplastic treatment. Most trials target preventive measures focusing on non-AIDS-defining cancers. However, treatment trials for the optimal management of people living with HIV and non-AIDS-defining cancer, including interventions such as immunotherapies, are needed to improve non-AIDS-defining cancer outcomes.

Introduction

HIV and malignancies have been linked since the first clinical descriptions of a cluster of Kaposi sarcoma cases in 1981, which would eventually be identified as AIDS.[1] Subsequently, additional malignancies, including some types of non-Hodgkin lymphoma and cervical cancer, were included in the case definition for AIDS and, together with Kaposi sarcoma, were defined as AIDS-defining cancers. However, as the epidemiology of HIV disease has evolved, particularly with the advent of antiretroviral therapy (ART), the incidence and morbidity of AIDS-defining cancers has decreased, whereas morbidity and mortality that is associated with non-AIDS defining cancers has increased.[2,3] The increased burden of non-AIDS-defining cancers is reflected by changes in the patterns of mortality for people living with HIV. Data for the US population-based HIV/AIDS Cancer Match (HACM) Study showed increases in the proportion of deaths that were attributable to non-AIDS-defining cancers between 2001–05 (ie, 7·2%) and 2011–15 (ie, 11·8%), despite stability in the proportions of deaths that were attributable to AIDS-defining cancer (ie, 5% across time periods).[4] Understanding the changing patterns of both AIDS-defining and non-AIDS-defining cancers will ultimately direct screening and treatment strategies to ensure optimal outcomes for people living with HIV. This Review will focus on the epidemiology, outcomes, and current clinical trials for solid-tumour non-AIDS-defining cancers that are virally and non-virally mediated (excluding Hodgkin lymphoma) in people living with HIV.

Epidemiology in people living with HIV

The cause of non-AIDS-defining cancers in people living with HIV is complex and might be related to a combination of the ageing population of people living with HIV;[5] co-infections with oncogenic viruses;[6] increased rates of tobacco, substance,[7] and medication use;[8] and HIV-associated metabolic disturbances.[9] For example, cigarette smoking is more frequent among people living with HIV compared with people who are negative for HIV in many

regions and most likely contributes to increased risk of several tumour types.[10] Modulation of oncogenic viral co-infections in people living with HIV, such as human papillomavirus, hepatitis B, and hepatitis C, is also linked to increased risks of virally mediated cancers, such as anal and liver cancers.[11]

Direct influence of HIV disease severity has been implicated in increased risk for many non-AIDS-defining cancers; HIV viral suppression was broadly associated with decreased non-AIDS-defining cancer risk in a national study of US veterans.[12] Similarly, the presence of an AIDS diagnosis, CD4 count less than 200 cells per μL after 6 months on ART, low nadir CD4 cell count, and long periods of low CD4 cell counts have been associated with increased standardised incidence ratios (SIRs) for some non-AIDS-defining cancers in population-based studies.[11,13,14] Beyond decreased CD4 T-cell immunity as a result of HIV infection, decreased CD4:CD8 ratio has also shown predictive value as a biomarker of non-AIDS-defining cancer risk in a large HIV cohort setting.[15] In summary, non-AIDS-defining cancer risk in people living with HIV is attributable to a combination of traditional risk factors (eg, age and smoking), oncogenic co-infections, and HIV disease management.

Table 1 summarises the risks of non-AIDS-defining cancers that are virally and non-virally associated in people living with HIV compared with people who are negative for HIV by geographical region. Notably, the magnitude and direction of the association between rates of HIV and non-AIDS-defining cancer differs by tumour site, and these associations do not directly parallel cancer burden. For example, even for cancers that do not occur more frequently in people living with HIV compared with people who are negative for HIV (eg, SIR ≤1 for prostate cancer in most studies, with the exception of two studies in table 1), the improved life expectancy resulting from use of ART to treat HIV has translated into higher absolute numbers of people living with HIV reaching ages where such tumours are more common. On the basis of these changing epidemiological trends and estimates of the population dynamics of US people living with HIV, Shiels and colleagues[5] used a model projecting the expected cancer burden (or absolute number of cases) of US people living with HIV in 2020 and 2030, which showed that prostate cancer is now the most prevalent cancer among people living with HIV, followed by lung cancer, and that this trend towards a growing burden of non-virally mediated non-AIDS-defining cancer in people living with HIV will continue during the next decade.

Incidence and risk of non-AIDS-defining cancer in people living with HIV

North America and Europe

The HACM Study has been a rich source of US population-based data regarding cancer risk for people living with HIV during the ART era. By linking data from more than 440 000 people living with HIV to state cancer registry data, the HACM Study has provided contemporary (ie, 1996–2012) risk estimates for non-AIDS-defining cancers in people living with HIV compared with people who are negative for HIV(table 1). Overall increased risk for non-AIDS-defining cancers among people living with HIV has been driven by increased incidence of specific cancer types. People living with HIV have a markedly increased risk of anal cancer; tumours with known causal co-infections, such as liver cancer; and other human papillomavirus-associated malignancies.[11] Several common cancers with no known

co-infection were also identified more frequently in the setting of HIV, including cancers of the lung, larynx (SIR 2·11), and pancreas (SIR 1·13). The incidence of breast cancer and prostate cancer, the two most common cancers among US women and men, were decreased in people living with HIV in the HACM data, a finding that has been replicated in other cohorts.[11,26]

European studies have reported similar incidence patterns and projections of non-AIDS-defining cancer to the USA. The EuroSIDA study (n=15 648), a large cohort of people with HIV with substantial representation of central and eastern Europe, also projected continued growth of the burden of non-AIDS-defining cancer (particularly non-virally mediated or ageing-related types) through the next decade.[27] Table 1 shows the findings of several of the European cohorts, including the Swiss HIV cohort[18] and the French Hospital Database on HIV study,[16] which have compared non-AIDS-defining cancer incidence rates in their participants to expected cancer rates in the general population.

Africa

An increase in the incidence of non-AIDS-defining cancers among people living with HIV relative to people who are negative for HIV has been shown in African countries. Uganda's AIDS-Cancer Registry Match study showed a more than two-times excess of non-AIDS-defining cancers overall among people living with HIV. In addition to the cancers that are listed in table 1, cancers of the conjunctiva (SIR 4·0 [95% CI 1·5–8·7]), kidney (16·0 [1·8–58·0]), thyroid (5·7 [1·1–16·0]), and uterus (5·5 [1·5–14·0]) were notably increased in incidence among people living with HIV.[20] However, a Nigerian study with a similar registry-linkage method did not observe higher rates of non-AIDS-defining cancers for people living with HIV relative to the population who were negative for HIV.[19] The largest African study on incidence of non-AIDS-defining cancer from South Africa used a probabilistic match of an HIV registry (ie, 95 279 people living with HIV) to a national cancer registry. Investigators did not find an overall increase in non-AIDS-defining cancers in people living with HIV compared with people who were negative for HIV, although they did note higher risk of anal cancer and lower risks of lung, breast, and prostate cancer in people living with HIV than in people who were negative for HIV.[21]

The burden of non-AIDS-defining cancer in women and children has received more attention in studies from Africa. A registry-linkage study in South Africa of cancers in children with HIV showed that children with HIV were at high risk of developing cancer overall. Most cancers were AIDS-defining cancers, although non-AIDS-defining cancers had an incidence rate of 17 cases per 100 000 person-years. ART use for HIV management substantially lowered cancer risk (hazard ratio [HR] 0·29 [95% CI 0·09–0·86]) in this study, whereas children with severe or advanced immunodeficiency at enrolment were more likely to develop cancer compared with children with mild or no immunodeficiency (3·54 [1·05–11·79]).[28]

Latin America

The expansion of ART use in Latin America has been associated with an increase in the burden of non-communicable diseases among an ageing population of people living

with HIV. Data from the large Caribbean, Central and South America Network for HIV Epidemiology showed that 24% of people living with HIV in Latin America were older than 50 years,[29] and non-AIDS-defining cancers represented 28% (219 of 783) of all cancers reported, with 65% (142 of 219) of cancers occurring between 2008 and 2015.[30] A retrospective study of non-AIDS-defining cancers in people living with HIV from Mexico reported that Hodgkin lymphoma (35% [35 of 101]) and anal cancer (16% [16 of 101]) were the most frequent cancers in men, while vulvar or vaginal cancers (54% [14 of 26]) and breast cancer (27% [7 of 26]) were the most frequent in women.[31]

Regional studies of cancer risk for people living with HIV in Latin America are scarce. In a population-based registry linkage study from São Paulo, most non-AIDS-defining cancers related to viruses occurred at increased rates in people living with HIV compared with the general population. The most prevalent cancers were anal cancer (SIR 33·02 in men and 11·21 in women), liver (4·35 in men and 4·84 in women), and cancers of the vulva or vagina (6·78 in women), and non-virally mediated non-AIDS defining cancers, such as lung cancer (2·24 in men and 2·60 in women) and CNS cancers (1·92 in men and 3·48 in women).[22]

Asia-Pacific

Despite a relatively low prevalence of HIV in Asia-Pacific, the region has the second largest population living with HIV, with 5·8 million people. Several large studies of cancer incidence have shown a growing prominence of non-AIDS-defining cancers among people living with HIV in this region. A study of 32 575 people living with HIV in Pune, India, (ie, 1996–2008) identified 613 patients with cancer, with 86% (530 of 613) of tumours being non-AIDS-defining cancers. There was an increased risk of breast, colorectal, oral, oesophageal, stomach, anal, penile, eye, and CNS cancers and leukaemia in people living with HIV, but not bowel, testis, prostate, or ovarian cancer; lymphocytic leukaemia; or melanoma.[32] A match of HIV and cancer surveillance databases for 399 451 people living with HIV in China (ie, 2008–12) showed that non-AIDS-defining cancers overall were diagnosed at nearly three-times higher rates in people living with HIV compared with people who were negative for HIV.[23]

Increased risk of non-AIDS-defining cancer for people living with HIV in China is most likely related to a substantial burden of risk factors in this population; a meta-analysis of cancer risk factors among Chinese people living with HIV reported that 41% of people were current smokers, 30% of people consumed alcohol, 24% of people were overweight or had obesity, and over a third of people had viral hepatitis.[33] A study of 1282 incident cancers in 15 269 people living with HIV from Taiwan (ie, 1998–2009) reported markedly increased incidence rates in people living with HIV compared with the general population in Taiwan for non-AIDS-defining cancers that were both virally and non-virally mediated.[24] A longitudinal study of 1001 people living with HIV in Japan observed a 6·4% 10-year cumulative incidence of non-AIDS-defining cancers, with an increased risk of liver, colon, and stomach cancer compared with the general population.[34] Finally, an Australian National HIV/AIDS Registries and Australian National Cancer Statistics Clearing House Linkage Study from the early ART era also identified incidence patterns of non-AIDS-defining cancer that were similar to contemporaneous North American and European reports.[25]

Outcomes in people living with HIV

Large HIV cohort studies and population-based analyses have shown that people living with HIV often have increased overall and cancer-specific mortality relative to the general oncology population (table 2). One of the first population-based studies to examine cancer-specific outcomes in people living with HIV in the USA reported that patients with non-small-cell lung cancer in the HACM Study were less likely to be administered cancer treatment.[39] A later article from the HACM Study noted increased cancer-specific mortality in people living with HIV compared with people who were negative for HIV (table 2) for multiple non-AIDS-defining cancer types (eg, cancer of the lung, colorectum, pancreas, breast, larynx, and prostate and melanoma), even after accounting for cancer stage and initiation of first-line treatment.[35] Data for more than 6 million US patients with cancer in the National Cancer Database further suggested that living with HIV was associated with poor cancer prognosis. Increased overall mortality was observed for 13 tumour sites, despite adjustment for cancer stage and treatment, health insurance, and type of cancer facility.[37] An adverse effect of HIV on patient outcomes that is independent of health-care access was further supported by the Kaiser Permanente Northern California and Southern California study reporting increased disease-specific mortality in people living with HIV with lung or prostate cancer compared with patients with cancer who were negative for HIV and enrolled in the same health system (table 2).[36] Finally, a study among Medicare-eligible individuals (ie, older than 65 years), a segment of the population that is of particular relevance for the ageing US population with HIV, focused on patients with non-AIDS-defining cancer who received stage-appropriate treatment and accounted for treatment timing and receipt of adjuvant therapies.[38] Among this older population, people living with HIV who were diagnosed with either breast or prostate cancer had higher rates of cancer-related deaths and higher rates of disease relapse or death after initial cancer therapy (HR 1·3–1·6) compared with the overall Medicare oncology population (table 2). Although population-based studies cannot establish the exact cause of poor cancer outcomes for people living with HIV, most US studies have shown persistently poor outcomes compared with patients who were negative for HIV with cancer. As the association between HIV and poor cancer outcomes is not unique to tumours with viral co-infections, it is probable that many factors contribute to this link, including disparities between cancer treatment, effect of HIV-related immune disturbances on tumour behaviour, and low underlying life expectancy or high comorbidities.

Treatment guidelines for people living with HIV

Notably, a survey of US radiation and medical oncologists showed that nearly 20% would not provide standard-of-care cancer treatment to people living with HIV, and there was an association between the likelihood of providing standard of care and oncologists' knowledge gaps regarding the safety and efficacy of care treatments for people living with HIV.[40] Since then, the US National Comprehensive Cancer Network has developed specific guidelines for cancer care in people living with HIV, which state that, with few exceptions, people living with HIV with good performance status should be offered guideline-based cancer treatments and that oncologists should work closely with infectious disease physicians and pharmacists to manage potential drug interactions and side-effects.[41] The importance of collaboration

between oncologists and infectious disease physicians is further emphasised by findings in US HIV cohorts that HIV disease severity can affect mortality in patients with cancer.[42,43]

In addition to cancer treatment considerations, people living with HIV might also have unique considerations affecting the benefits and harms of cancer screening, such as increased (or decreased) cancer risk, differential life expectancy, altered performance on screening test, and unique cancer therapy outcomes.[44] However, HIV-specific cancer screening data and guidance are scarce. European and US guidelines recommend cancer screening that is appropriate for age and risk factor and human papillomavirus vaccination (if indicated on the basis of age—ie, for people younger than 27 years, and possibly up to age 45 years) for people living with HIV.[45,46] Future efforts to develop HIV-specific data for cancer screening to guide clinical implementation of accepted screening tools are warranted. Notably, research efforts are ongoing to improve understanding of screening in the context of HIV for both anal cancer and lung cancer, and these efforts are described later in this Review.

Special consideration for specific tumour types

Potentially virally mediated cancers

Squamous cell carcinoma of the anus is one of several non-AIDS-defining cancers with a causal association with human papillomavirus. The relative risk of squamous cell carcinoma of the anus for people living with HIV compared with people who are negative for HIV is the highest among non-AIDS-defining cancers. The increased incidence of squamous cell carcinoma of the anus in people living with HIV compared with people who are negative for HIV ranged from SIRs of 19·1 to 79·3 in US and European studies (table 1). Indeed, 1% of all women who are diagnosed with squamous cell carcinoma of the anus and 28% of all men diagnosed with squamous cell carcinoma of the anus in the USA are people living with HIV.[47] Because cervical cancer and squamous cell carcinoma of the anus are both associated with human papillomavirus and share similar natural histories, including detectable high-risk human papillomavirus infections and dysplastic precursor lesions, professional organisations have recommended annual anal cytology screening for people living with HIV, followed by high-resolution anoscopy for triage of abnormal cytology results.[48]

Perhaps as a result of increased awareness of squamous cell carcinoma of the anus among oncologists and infectious diseases specialists, and perhaps as a result of earlier detection from screening programmes, studies have shown similar survival from squamous cell carcinoma of the anus between people living with HIV and people who are negative for HIV (table 2). The locoregional progression rate for people living with HIV has ranged from 10–30%,[49,50] but reports from the US Veterans Health Administration system have shown higher proportions of severe haematological toxicity and non-cancer death in people living with HIV compared with people without HIV.[51] As a result of these high rates of toxicity, the US National Comprehensive Cancer Network guidelines for people living with HIV suggest that radiotherapy should be delivered via an intensity-modulated radiation therapy technique.[41] Additionally, a single phase 2 trial of treatment of locoregional squamous cell carcinoma of the anus that was specific to people living with HIV has been published,[52] evaluating chemoradiotherapy with cisplatin plus fluorouracil and cetuximab accompanied

by 45–54 Gy of external beam radiotherapy. This trial noted survival that was consistent with outcomes for people who were negative for HIV in previous studies and some potential evidence of decreased locoregional progression with the addition of cetuximab. Toxicity was still substantial, with 27% (12 of 45) of patients having grade 4 events and 4% (2) of patients with treatment-associated deaths.[52] Other late ART-era data suggest that immune restoration might be associated with a decrease in standard toxicity that is related to 5-fluorouracil-based chemoradiation therapy.[53]

Cancers of the head and neck are more frequent among people living with HIV than in the general population due to associations with tobacco use and human papillomavirus infection.[54] Squamous cell carcinoma of the oropharynx is often differentiated from non-oropharyngeal head and neck cancers due to a stronger association with human papillomavirus infection. People living with HIV have a higher incidence of both squamous cell carcinoma of the oropharynx and non-oropharyngeal head and neck squamous cell carcinoma than do people who are negative for HIV (table 1).[11,17,55]

Similar to the general population, incidence of squamous cell carcinoma of the oropharynx in people living with HIV has increased from 6·8 cases per 100 000 person-years in 1996–2000 to 11·4 per 100 000 person-years in 2006–09.[55] To date, few studies have explored the interaction between human papillomavirus and HIV in oropharyngeal cancer tumours, although it has been shown that people living with HIV generally have a higher prevalence of oral human papillomavirus infection than do people who are negative for HIV.[56,57] Estimates for the proportion of oropharyngeal cancer that are attributable to human papillomavirus among people living with HIV range from 55% to 80%, depending on the population.[58] Additionally, after treatment, people living with HIV with human papillomavirus-positive squamous cell carcinoma of the oropharynx might not have the same increased survival as people with human papillomavirus-positive squamous cell carcinoma of the oropharynx in the general population, and studies evaluating treatment tolerance and completion are ongoing.[59]

Other squamous cell cancers that have been shown to be associated with high-risk mucosal human papillomavirus include vaginal, vulvar, penile, and conjunctival (ie, ocular surface squamous neoplasia) cancers. Additionally, both non-mucosal and genital high-risk human papillomavirus types have been linked to the development of non-melanoma skin cancers.[60] The South African National Cancer–National Health Laboratory Service match study noted increased risk for penile cancers (OR 2·35 [95% CI 1·85–2·99]), vulvar cancers (1·94 [1·67–2·25]), and ocular surface squamous neoplasia (21·5 [16·3–28·4]) compared with individuals who were negative for HIV.[21] The Uganda AIDS-Cancer Registry Match study identified an increased risk for ocular surface squamous neoplasia (SIR 4·0 [95% CI 1·5–8·7]) in people living with HIV.[20] For non-melanoma skin cancers, a study in Kaiser Permanente Northern California noted that people living with HIV had a higher risk of non-melanoma skin cancers compared with controls who were negative for HIV (HR 1·15 [95% CI 1·02–1·31]); people living with HIV had 2·1 times the risk for basal cell carcinoma and 2·6 times the risk for squamous cell carcinoma compared with controls who were negative for HIV, and low CD4 cell counts were associated with a high risk for squamous cell carcinoma but not basal cell carcinoma.[61]

Globally, the epidemiology of cirrhosis and hepatocellular carcinoma in patients with HIV is dominated by the burden of chronic viral hepatitis B and hepatitis C infection. As hepatitis B and hepatitis C infection are more prevalent in people living with HIV than in the general population (due to common modes of transmission), [6] the incidence of hepatocellular carcinoma has consistently been higher among people living with HIV compared with individuals who are negative for HIV, with the exception of studies in sub-Saharan Africa (table 1). Additionally, studies have noted that low CD4 cell counts are associated with increased incidence of hepatocellular carcinoma in patients with HIV and hepatitis C co-infection, further suggesting a link between HIV and risk of hepatocellular carcinoma.[62] Outcomes can differ for hepatocellular carcinoma in the setting of HIV; people living with HIV and hepatocellular carcinoma in the USA have higher mortality compared with patients with hepatocellular carcinoma who are negative for HIV (table 2). Hepatocellular carcinoma is one of the few tumours for which global survival data are also available; a 24% increase in mortality from hepatocellular carcinoma in people living with HIV was observed in the Liver Cancer in HIV and ITA.LI.CA study groups.[63] Thus, people living with HIV and cirrhosis might be a particularly important group to encourage participation in guideline-based screening programmes for hepatocellular carcinoma.

Non-virally mediated cancers

Lung cancer is the leading cause of cancer death for people with HIV.[44] Higher rates of cigarette smoking among people with HIV compared with people who are negative for HIV are a major contributor to the burden of lung cancer in this population. Population-based microsimulation projections estimate that, given current smoking trends in the US population living with HIV, 9·3% of people living with HIV aged 20–64 years will die of lung cancer.[64] This substantial risk of death from lung cancer is also due to increases in risk of lung cancer that are independently associated with HIV infection. Large cohort studies in the USA and Europe have reported point estimates for risks for lung cancer after adjustment for smoking ranging from 1·7 to 2·4.[65,66] Despite these enhanced risks of lung cancer for people living with HIV, incidence might be decreasing over time, as reflected in analyses of the NA-ACCORD, an international collaboration of 25 different HIV cohorts, which showed trends of decreasing incidence rates in time periods until 2009.[67]

Cancer-specific survival has been shown to be worse for people living with HIV with lung cancer than for people who are negative for HIV with lung cancer in the USA (table 2). Although smaller case series have suggested potential increases in complications of treatment for lung cancer for people living with HIV, a national US study of surgical outcomes did not identify increases in short-term mortality or major complications within 1 month of surgery.[68] Evaluations of cytotoxic chemotherapy side-effects in patients with lung cancer have also been scarce, but a cohort from France observed more deaths than expected and potential increases in toxicity that were associated with use of HIV protease inhibitors.[69] A single clinical trial was published of chemotherapy for advanced lung cancer in people living with HIV: a phase 2 study in France (n=61) evaluated safety and efficacy for carboplatin plus pemetrexed with pemetrexed maintenance. The study showed survival and outcomes similar to those expected in people who were negative for HIV, but haematological toxicity was higher in patients with AIDS than in patients

who were negative for HIV.[70] Early results for people living with HIV who were treated with immunotherapy for advanced lung cancer have not suggested any excess in adverse events compared with the general oncology population.[71] However, the US National Comprehensive Cancer Network suggests caution during use of immunotherapy in people with Kaposi sarcoma- associated herpesvirus infection, because there might be increased risk of inflammatory syndromes that are related to Kaposi sarcoma-associated herpesvirus, such as multicentric Castleman disease or Kaposi sarcoma-associated herpesvirus-associated inflammatory cytokine syndrome.[41]

Screening for lung cancer with low-dose CT has been widely advocated for some heavy smokers due to large randomised trials showing benefits on mortality from lung cancer.[72] As false positive low-dose CT screens can lead to a high risk of harms related to screening (eg, unnecessary lung biopsy), an initial concern is that a greater prevalence of incidental findings on lung imaging for people living with HIV than for people who are negative for HIV might affect screening efficacy. Although no randomised controlled trials of low-dose CT screening have been done specifically for people living with HIV, data for prospective cohort studies and microsimulation models have suggested that screening is likely to have similar benefit and harm profiles for people living with HIV who meet population-based screening criteria.[73,74]

Unlike with other non-AIDS-defining cancers, HIV has not been associated with an increased risk of prostate carcinoma. In fact, registry-linkage studies from multiple continents have observed lower prostate cancer rates in people living with HIV than in people who are negative for HIV. Despite this lower risk, there is a substantial burden of prostate cancer among men with HIV compared with men who are negative for HIV (table 1), because the lower risk of prostate cancer in the setting of HIV does not counteract the rapidly increasing numbers of men older than 65 years who will develop prostate cancer, thus the actual burden (ie, case count) of prostate cancer in men with HIV continues to increase.[5] Notably, the US-based HACM Study identified a lower risk of prostate cancer in men with HIV for both early stage disease that was likely to be detected by screening and for late-stage tumours that were less likely to have been identified during screening than for men who were negative for HIV, showing that infrequent screening is not the cause for the lower risk of prostate cancer among men with HIV.[11] Despite potentially lower incidence rates, men with HIV appear to have worse outcomes of prostate cancer, with increased prostate cancer-specific mortality compared with men without HIV, as shown in multiple US databases (table 2). However, few data that are specific to tumour severity or non-US populations have been published, emphasising a large knowledge gap.

It is problematic that there has been little research that is specific to prevention or treatment of prostate cancer for men with HIV. No treatment trials that are specific to men with HIV have been published. A US population-based study reported no differences in major postoperative complications for men with HIV (n=546) undergoing robotic-assisted laparoscopic prostatectomy compared with men who were negative for HIV.[75] Before this study, a 2019 systematic review collected all available published treatment data for localised prostate cancer in men with HIV (n=202), concluding that no specific treatment recommendations could be made for this population due to a paucity of available data.[76]

Screening for prostate cancer is controversial for men, irrespective of HIV status, as the balance of potential harms and mortality benefits that are associated with early detection and treatment are complex. As a result, the US Preventive Services Taskforce has given screening a C-level recommendation, advocating for shared decision making and not screening individuals who have no preference for screening. The Infectious Diseases Society of America HIV management guidelines echo these recommendations.[46]

Although colon cancer is one of the cancers that is commonly associated with ageing in high-income countries, in general, all but three studies in table 1 showed higher SIRs for colon cancer in people living with HIV. However, population-based US outcomes studies have shown that people living with HIV who also had colorectal cancer had poorer survival than did individuals who were negative for HIV (table 2). The reasons for the differences in outcome are unclear, but people living with HIV appear to be diagnosed with colorectal cancer at similar (and even slightly earlier) stages of disease compared with individuals who are negative for HIV.[37] There are no differences in screening and treatment guidelines for people living with HIV compared with individuals who are negative for HIV.

On the basis of projections by use of combined International Agency for Research on Cancer–Global Cancer Observatory data, there were an estimated 6325 women living with HIV in 2012 who were diagnosed with breast cancer, 75% (4744 of 6325) of whom were in sub-Saharan Africa and 70% (4428 of 6325) of whom were diagnosed before age 50 years.[77] HIV has been associated with a notably lower risk of breast cancer compared with the general population in European and sub-Saharan African cohorts and meta-analyses,[78–82] although smaller studies in India and Taiwan reported higher risk in women living with HIV than in the general population.[32,83] The US-based HACM Study reported risks separately by disease stage and noted lower risk of breast cancer for women living with HIV for early stage (SIR: 0·63) but not late-stage (SIR: 0·94) disease, compared with the general population.[11]

Presentation of breast cancer can differ in the setting of HIV infection. A meta-analysis of 3174 women with HIV from the USA and sub-Saharan Africa noted that women living with HIV were nearly twice as likely (pooled odds ratio 1·76) to present with late-stage disease compared with women without HIV.[78] Women living with HIV from sub-Saharan Africa were also less likely to have ER-positive and HER2 (ERBB2)-negative tumours (pooled odds ratio 0·81). Finally, patient outcomes after diagnosis differ; women living with HIV and breast cancer in the USA have higher mortality than patients with breast cancer who do not have HIV (table 2), and this finding was echoed by the group of four studies (of 315 women living with HIV) from sub-Saharan Africa that were reported in Brandão and colleagues' meta-analysis (pooled HR 1·58).[78] Smaller studies from Italy,[84] Brazil, [85] and Malawi [86] also showed that women living with HIV had not only higher mortality after a diagnosis of breast cancer, but also were less likely to have complete pathological response with neoadjuvant chemotherapy and were more likely to have chemotherapy-related toxicity than were women without HIV.[87,88] Outcome disparities and poor treatment tolerability were commonly attributed to drug interaction between cytotoxic chemotherapy and antiretroviral drugs.

Similar to lung cancer, smoking and tobacco use has been a large contributor to an increased risk of non-oropharynx head and neck cancer among people living with HIV.[59] Even after adjustment for smoking, HIV has been consistently associated with an increased risk of non-oropharyngeal head and neck squamous cell carcinoma.[55] However, as smoking rates in the USA have declined, the incidence of non-oropharyngeal head and neck squamous cell carcinoma among people living with HIV has also decreased (ie, 41·9 cases per 100 000 people with HIV in 1996–2000 to 29·3 cases per 100 000 people with HIV in 2006–09).[55] Large studies on outcomes for patients with HIV and head and neck squamous cell carcinoma are scarce, but a national US study of veterans reported that, in contrast to usual prognostic patterns, overall survival was worse in people living with HIV with oropharyngeal head and neck squamous cell carcinoma compared with in people living with HIV with non-oropharyngeal cancer.[59] To date, no large studies have explored treatment complications and tolerability among people living with HIV with head and neck squamous cell carcinoma.

Clinical trials and global research into treatments for patients with non-AIDS-defining cancer

Few trials for cancer treatments have been done to provide guidance on HIV-specific care for patients with non-AIDS-defining cancer. Although people living with HIV have previously been excluded from participating in cancer clinical trials, there have been efforts to scrutinise standard exclusion of people living with HIV for trials of novel cancer therapy, such as the National Cancer Institute-sponsored phase 3 trial of nivolumab use after combined modality therapy for patients with high-risk stage II–IIIB anal cancer.[89] Additionally, phase 1 studies that were focused on HIV have shown that single-agent immunotherapies, including pembrolizumab and durvalumab, are safe in people living with HIV who have CD4 counts over 100 cells per mm^3.[71,90] Studies focusing on the safety and efficacy of combinations of novel immunotherapies in people living with HIV, and drug interactions for targeted therapies and ART, might still be needed. Additionally, given the poor treatment outcomes and potentially unique biology of some cancers in people living with HIV, there is also a need for studies to improve understanding of the underlying causes of poor outcomes, which could help to identify differentiated or tailored treatment targets in this population. Of the active trials for cancer prevention and treatment specifically for people living with HIV that are listed in the US National Library of Medicine clinical trials database (table 3), nine (53%) of 17 trials focus on cancer prevention, such as the ANCHOR study, a large randomised trial to establish the effectiveness of screening detection and treatment of anal high-grade intraepithelial lesions in prevention of anal cancer (NCT02135419).

According to UNAIDS, of the estimated 37 827 000 people living with HIV worldwide, more than 75% of people live in Africa, Latin America, or Asia-Pacific regions (table 4). However, most studies of incidence, prevalence, and outcomes of non-AIDS-defining cancer, and almost all studies of screening and treatment for non-AIDS-defining cancer, have been done in North America and western Europe. As shown in table 3, all except two clinical trials (ie, 15 [88%] of 17) were based in North America or western Europe,

with only one based in Africa. Most current clinical trials in sub-Saharan Africa focus on AIDS-defining cancers. Improving the research capacity is urgently needed to serve the growing population of people living with HIV who have non-AIDS-defining cancers in low-income and middle-income countries. In particular, research evaluating the effect of HIV on early cancer detection for common non-AIDS-defining cancers (eg, lung, oesophageal, gastric, and human papillomavirus-related cancers and hepatocellular carcinoma), evaluation of novel treatments, and expanding pathology and supportive care infrastructure will inform next steps in improving patient care.

Conclusion

As the global population living with HIV ages, non-AIDS-defining cancers will continue to be a major clinical issue for this population. Although this Review is limited by the small number of clinical trials for treatment of non-AIDS-defining cancers, and the fact that most of the studies were oriented to high-income countries, it shows the unique demographics, incidence, behaviours, and outcomes for non-AIDS-defining cancers among people living with HIV. In turn, these factors affect preventive measures, such as early cancer detection, and cancer management, necessitating investigation targeted to people living with HIV. Despite the fact that people living with HIV have been previously excluded from oncology clinical trials, several important international trials specifically evaluating prevention and treatment of non-AIDS-defining cancers for people living with HIV are underway, with a focus on immunotherapy, including those from the AIDS Malignancy Consortium. Finally, given the growing burden of non-AIDS-defining cancers in people living with HIV in low-income and middle-income countries, funding priorities should be focused on building research capacity and increasing clinical research activities to support evidence-based prevention and treatment focused on non-AIDS-defining cancers.

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Search strategy and selection criteria

We searched PubMed for articles that were published between Dec 1, 2000, and Dec 1, 2020, including the words “HIV”, “cancer”, “non-AIDS defining cancer”, and “malignancy”. We also identified articles through searches of the authors’ own files. For the search on comparing risks of non-AIDS-defining cancer between people living with HIV and controls who were negative for HIV, we included articles if they were peer-reviewed, published in English, reported standardised incidence ratio or odds ratio for all cancers in the study, and included over 1000 individuals. For the search on comparing non-AIDS-defining cancer outcomes between people living with HIV and controls who were negative for HIV, we used “outcome” or “survival” as additional search terms and included articles if they were peer-reviewed, published in English, reported either overall mortality or cancer-related mortality, or both, published in 1996 or later, and included data for over 200 patients with cancer and HIV. For the active clinical trials that included people living with HIV, we searched ClinicalTrials.gov for all trials as of Dec 1, 2020. The search was limited to studies whose recruitment status was listed as “not yet recruiting”, “recruiting”, or “active, not recruiting” (but active not recruiting studies with posted results were excluded). The studies included prospective trials that did not exclude people living with HIV and were designed to evaluate biomedical interventions for prevention, treatment, or supportive care of non-AIDS-defining cancer. We excluded studies that focused on only behavioural interventions or descriptive or prognostic factors.

Table 1:

Large studies of incidence of non-AIDS-defining cancers in people living with HIV compared with people who are negative for HIV by region and cohort

	Years	Number of people living with HIV	Overall SIR or OR for non-AIDS-defining cancer (95% CI)	SIR or OR for non-virally mediated cancer (95% CI)					SIR or OR for virally mediated cancer (95% CI)		
				Lung cancer	Prostate cancer	Breast cancer	Colon cancer	Anal cancer	Liver cancer	Oropharynx	Non-oropharynx head and neck squamous cell carcinoma
North America and Europe											
US HIV/AIDS Cancer Match Study[11]	1996–2012	448 258	1·21 (1·19–1·23)	1·97 (1·89–2·05)	0·48 (0·46–0·51)	0·63 (0·58–0·68)	0·61 (0·56–0·67)	19·06 (18·13–20·03)	3·21 (2·02–3·41)	1·64 (1·46–1·84	2·20 (1·98–2·45)
French Hospital Database on HIV[16]	2005–09	84 504	··	2·8 (2·5–3·1)	··	··	··	79·3 (69·5–90·1)	10·9 (9·6–12·3)	··	··
Dat'AIDS[17]	2010–15	44 642	··	0·7 (0·6–0·9)	0·6 (0·5–0·7)	0·6 (0·4–0·7)	··	··	3·8 (3·1–4·6)	1·1 (0·9–1·5) *	1·1 (0·9–1·5) *
Swiss HIV Cohort[18]	2002–06	9429	2·2 (1·8–2·7)	2·6 (1·3–4·6)	1·3 (0·4–3·1)	0·9 (0·2–2·4)	0·3 (0·0–1·6)	49·9 (18·0–109·0)	6·1 (1·9–14·3)	2·1 (0·9–4·5) *	2·2 (0·9–4·5) *
Africa											
Nigerian AIDS-Cancer Match[19]	2005–12	17 826	··	··	0·4 (0·0–16·9)	1·6 (0·2–3·0)	··	0·6 (0·0–17·8)	0·5 (0·0–5·1)	··	··
Uganda AIDS-Cancer Registry Match[20]	1988–2002	12 607	2·8 (3·3–4·4)	5·0 (1·0–15·0)	2·9 (0·3–11·0)	1·9 (0·8–3·7)	··	··	2·1 (0·4–6·0)	··	··
South Africa National Health Laboratory Service-Cancer Registry Linkage Study[21]	2004–14	95 279	OR 0·26 (0·25–0·26)	OR 0·52 (0·48–0·57)	OR 0·85 (0·76–0·95)	OR 0·43 (0·41–0·45)	OR 0·43 (0·38–0·47)	OR 1·63 (1·33–2·00)	OR 0·45 (0·39–0·53)	OR 0·55 (0·50–0·59)	OR 0·56 (0·49–0·64) †
Latin America											
São Paulo AIDS-Cancer Linkage Study[22]	1997–2012	87 109	1·87 (1·74–2·01)	2·24 (1·71–2·92)	1·00 (0·76–1·33)	1·30 (0·42–4·04)	1·60 (1·24–2·06)	33·02 (25·80–42·27)	4·35 (2·74–6·91)	2·96 (1·75–4·99)	1·70 (1·12–2·58) †
Asia-Pacific											

	Years	Number of people living with HIV	Overall SIR or OR for non-AIDS-defining cancer (95% CI)	SIR or OR for non-virally mediated cancer (95% CI)					SIR or OR for virally mediated cancer (95% CI)		
				Lung cancer	Prostate cancer	Breast cancer	Colon cancer	Anal cancer	Liver cancer	Oropharynx	Non-oropharynx head and neck squamous cell carcinoma
China's National HIV/AIDS Surveillance Program and National Free Antiretroviral Treatment Program Study[23]	2008–12	399 451	2·9 (2·8–3·1) for men, 2·1 (1·9–2·2) for women	4·8 (4·4–5·1), 4·2 (3·5–5·0)	0·6 (0·3–1·2)	1·6 (0·2–5·8), 0·3 (0·2–0·4)	1·5 (1·2–1·8), 1·1 (0·7–1·5)	2·9 (0·3–10·5), 0·0 (0·0–19·7)	3·9 (3·6–4·2), 5·2 (4·2–6·5)	1·3 (0·7–2·2), 1·2 (0·3–3·1)	··
Taiwan's National Health Insurance Research Database[24]	1998–2009	15 269	··	8·52 (6·82–10·63)	3·48 (2·03–5·57)	0·59 (0·31–1·03)	7·53 (5·99–9·44)	19·10 (12·80–27·50)	5·50 (4·54–6·59)	5·40 (3·25–8·42)	7·82 (3·58–14·86)†
Australian National HIV/AIDS Registries and Australian National Cancer Statistics Clearing House Linkage Study[25]	2000–04	20 232	··	1·10 (0·62–1·82)	0·27 (0·11–0·52)	··	0·38 (0·16–0·75)	32·11 (19·33–50·14)	2·96 (1·19–6·10)	1·65 (0·66–3·39)	··

SIR=standardised incidence ratio. OR=odds ratio.

*Provided summary results for all head and neck tumours.

†Larynx.

Table 2:

Outcomes after cancer diagnosis for patients with HIV and patients who are negative for HIV from large US studies by cohort and type of cancer

	Cases among people with HIV	Deaths among people with HIV*	Overall death HR (95% CI)	Cancer-specific death HR (95% CI)
US HIV/AIDS Cancer Match Study† (1996–2010)[35]				
Lung	1058	907	1·85 (1·73–1·97)	1·28 (1·17–1·39)
Prostate	502	104	2·59 (2·14–3·14)	1·57 (1·02–2·41)
Breast	314	144	4·62 (3·92–5·45)	2·61 (2·06–3·31)
Colorectal	374	183	2·26 (1·95–2·61)	1·49 (1·21–1·84)
Liver	316	257	1·50 (1·32–1·70)	1·17 (0·99–1·39)
Anal	668	268	1·86 (1·60–2·16)	0·97 (0·75–1·25)
Head and neck‡	278	154	2·46 (2·09–2·88)	1·31 (0·94–1·83)
Kaiser Permanente Northern California and Southern California§ (1996–2010)[36]				
Lung	80	58	··	1·3 (1·0–1·7)
Prostate	150	9	··	2·1 (1·1–4·1)
Colorectal	53	12	··	1·4 (0·8–2·7)
Anal	120	27	··	1·6 (0·4–6·6)
National Cancer Database¶ (2004–14)[37]				
Lung	1908	1547	1·20 (1·14–1·26)	··
Prostate	1170	236	1·56 (1·37–1·77)	··
Breast	957	399	1·85 (1·68–2·04)	··
Colorectal	1524	903	1·58 (1·48–1·69)	··
Liver	515	422	1·29 (1·16–1·42)	··
Anal	764	319	1·34 (1·19–1·52)	··
Head and neck‖	353	194	1·66 (1·44–1·92)	··
Surveillance, Epidemiology and End Results-Medicare ** **(1996–2012)**[38]				
Lung	34	24	1·17 (0·79–1·75)	1·04 (0·62–1·76)
Prostate	170	63	1·58 (1·23–2·03)	1·65 (0·98–2·79)
Breast	50	24	1·50 (1·01–2·24)	1·85 (0·96–3·55)
Colorectal	34	20	1·73 (1·11–2·68)	1·68 (0·87–3·23)

Only those cancers that were assessed in each study are included. HR=hazard ratio.

*Deaths listed are deaths from any cause, except for Kaiser Permanente Northern California and Southern California, for which cancer deaths are listed.

†Data are from HIV and state cancer registry linkages in the states of Colorado, Connecticut, Georgia, Michigan, New Jersey, and Texas (USA). HRs were adjusted for cancer stage. Differences persisted after adjustment for type of first-line treatment that was initiated.

‡Head and neck cancer comprised of cancers of the oral cavity and pharynx.

§Data are from a large health-care system that is managed in CA, USA. HRs accounted for cancer stage, treatment type, and smoking.

¶Data are from a national hospital-based registry database. HRs account for cancer stage and treatment, receipt of health insurance, and cancer care facility type.

// Head and neck cancer comprised of cancers of the oral cavity, pharynx, and larynx.

** Data are from cancer registry linkage to Medicare claims for individuals ≥65 years. Data are limited to patients with non-advanced cancer who were receiving stage-appropriate treatment. Disease relapse is more likely in breast (HR=1·63 [95% CI 1·09–2·43]) and prostate (HR=1·32 [1·03–1·71]) cancers for people with HIV.

Table 3:

Ongoing clinical trials for screening and treatment of non-AIDS-defining cancer in people living with HIV

	Study name or topic	Cancer type	Country	Sponsor	Status	Type	Phase	People who are enroled or enrollment target, n	Intervention	Outcomes
NCT02823847	Non-invasive oral cancer screening	Oral cancer	USA	MD Anderson Cancer Center	Active, not recruiting	Screening	1	38	Screening; interview; carbon monoxide test; self-help materials	Positive predictive value for premalignant and malignant oral lesions
NCT03094286	Durvalumab in solid tumours	Solid tumours	Spain	Spanish Lung Cancer Group	Active, not recruiting	Treatment	2	20	Durvalumab	Number who received durvalumab; overall response rate; progression-free survival; overall survival rate
NCT03304093	Immunotherapy by nivolumab	Lung cancer	France	Intergroupe Francophone de Cancerologie Thoracique; French National Institute for Health and Medical Research–French National Agency for Research on AIDS and Viral Hepatitis	Active, not recruiting	Treatment	2	16	Nivolumab injection	Disease control rate; progression-free survival; overall survival rate
NCT04055142	Electrocoagulation *vs* topic sinecatechins *vs* topic cidofovir within the treatment to high-grade anal intraepithelial neoplasia	Anal cancer	Spain	Hospital Universitari Vall d'Hebron Research Institute	Not yet recruiting	Treatment	3	105	Electrocoagulation: cidofovir 1% topical ointment; sinecatechins 10% topical ointment	Percentage of patients with complete or partial regression of high-grade anal intraepithelial neoplasia at 10 weeks; number of patients with treatment-related adverse events; number of patients with analytical and clinical adverse events
NCT01822522	Cabozantinib s-malate for advanced solid tumours	Advanced solid tumours	USA	NCI	Active, not recruiting	Treatment	1	36	Cabozantinib s-malate laboratory biomarker analysis; pharmacological study	Incidence of adverse events; maximal tolerated dose; response rates

	Study name or topic	Cancer type	Country	Sponsor	Status	Type	Phase	People who are enroled or enrollment target, n	Intervention	Outcomes
NCT02135419	ANCHOR: topical or ablative treatment for anal high-grade squamous intraepithelial lesions	Anal Cancer; high-grade anal intraepithelial neoplasia	USA	AIDS Malignancy Consortium; NCI	Recruiting	Treatment and prevention	3	5058	Imiquimod; fluorouracil; infrared photocoagulation therapy	Time to anal cancer; incidence of adverse events; quality of life
NCT02437851	Surgery in treating patients with early stage anal canal or perianal cancer	Anal cancer	USA	AIDS Malignancy Consortium; NCI	Recruiting	Treatment	2	56	Therapeutic conventional surgery	Percentage of patients for whom treatment did not work at 2 years; percentage of patients with incident anal squamous cancers at sites other than the index anal cancer; percentage of patients for whom treatment did not work by 3 years; the rate of treatment-related adverse events
NCT02595866	Pembrolizumab for relapsed, refractory, or disseminated malignant neoplasms	Advanced cancer	USA	NCI	Recruiting	Treatment	1	60	Laboratory biomarker analysis; pembrolizumab	Frequency of adverse events; incidence of immune-related events of clinical interest
NCT02408861	Nivolumab and ipilimumab for relapsed or refractory classical Hodgkin lymphoma or solid tumours	Hodgkin lymphoma, advanced solid tumours	USA	NCI	Recruiting	Treatment	1	96	Ipilimumab; nivolumab	Maximum tolerated dose of nivolumab; objective response rate; immune function
NCT03499795	VGX-3100 for the treatment of human papillomavirus-16 or human papillomavirus-18 related anal or anal–perianal, high grade squamous intraepithelial lesion	Anal neoplasm	USA; Canada	Inovio Pharmaceuticals	Active, not recruiting	Treatment and prevention	2	22	VGX-3100; CELLECTRA 5PSP	Percentage of patients with no histological evidence of anal high grade squamous intraepithelial lesion and no evidence of human papillomavirus-16 or human papillomavirus-18 at week 36; number of local and systemic adverse events 7 days following each dose; number of adverse events
NCT02287961	Human papillomavirus	None	France	French National Institute for	Active, not recruiting	Screening	NA	500	Standard proctological	Evaluation of high-grade anal

	Study name or topic	Cancer type	Country	Sponsor	Status	Type	Phase	People who are enroled or enrollment target, n	Intervention	Outcomes
	infection and related anal lesions in HIV-positive men who have sex with men			Health and Medical Research–French National Agency for Research on AIDS and Viral Hepatitis					examination; high-resolution anoscopy; biopsies	lesions by high-resolution anoscopy; evaluation of anal human papillomavirus infection by DNA, RNA, and protein detection; quantification of spontaneous regression of high-grade anal lesions
NCT02059499	Imiquimod, fluorouracil, or observation for HIV-positive patients with high-grade anal squamous skin lesions	Anal intraepithelial neoplasia; anal high-grade squamous intraepithelial lesion	USA	AIDS Malignancy Consortium; NCI; The Emmes Company; University of Arkansas	Recruiting	Prevention	3	150	Imiquimod; fluorouracil; questionnaire administration; laboratory biomarker analysis	Proportion of participants with complete response (arm A and B); proportion of participants with spontaneous regression of anal high-grade squamous intraepithelial lesion
NCT03947775	HPV-SAVE: nine-valent human papillomavirus vaccine for high-grade anal dysplasia	Anal high grade intraepithelial neoplasia; anal cancer	Canada	University Health Network, Toronto; Merck Sharp & Dohme	Not yet recruiting	Treatment	1	206	Nine-valent human papillomavirus vaccination	The proportion of participants in each arm with biopsy-proven high-grade anal intraepithelial neoplasia; the geometric mean titres of antibody
NCT04141449	Multilevel intervention to improve timely cancer detection and treatment initiation	Cervical cancer; breast cancer; head and neck squamous cell carcinoma; vulvar cancer; anal cancer	Botswana	Brigham and Women's Hospital; Botswana Harvard AIDs Institute; Dana-Farber Cancer Institute	Not yet recruiting	Screening	2	1500	Potlako intervention; enhanced care	Duration of combined appraisal and help-seeking intervals; duration of diagnostic interval; duration of pretreatment interval
NCT04255849	Nine-valent human papillomavirus vaccine to prevent persistent oral human papillomavirus infection in men living with HIV	Human papillomavirus positive oropharyngeal squamous cell carcinoma	Brazil, Mexico, Puerto Rico	Weill Medical College of Cornell University; H Lee Moffitt Cancer Center and Research Institute; University of São Paulo	Not yet recruiting	Treatment and prevention	3	500	Nine-valent human papillomavirus vaccine (ie, types 6, 11, 16, 18, 31, 33, 45, 52, and 58); saline placebo	Antibodies against the 9 genotypes of the human papillomavirus vaccine; incidence of treatment-related adverse events; new human papillomavirus genotypes
NCT04563754	High resolution microendoscopy for	Anal high-grade squamous	USA	Baylor College of Medicine; Icahn School of	Recruiting	Screening and diagnosis	Other	200	Mobile high-resolution microendoscope	Performance characteristics: sensitivity, specificity,

	Study name or topic	Cancer type	Country	Sponsor	Status	Type	Phase	People who are enroled or enrollment target, n	Intervention	Outcomes
	people living with HIV	intraepithelial lesion		Medicine at Mount Sinai; William Marsh Rice University						positive predictive value, negative predictive values, and procedure time
NCT04587050	Screening for human papillomavirus and cervical cancer in young women with perinatally acquired HIV (SHiP)	Cervical cancer	UK	Imperial College London; Public Health England	Not yet recruiting	Screening	NA	80	Cervical cytology; testing for high-risk human papillomavirus types; human papillomavirus antibody titres	Prevalence of abnormal cervical cytology

NA=not applicable. NCI=National Cancer Institute.

Table 4:

HIV prevalence in 2019 by region

	Prevalence per 100 000 people (uncertainty bounds)	People living with HIV, n	Proportion of people living with HIV globally (n=37 827 000), %
Asia–Pacific	0·2 (0·1–0·2)	5 800 000	15·3%
Caribbean	1·1 (0·9–1·3)	330 000	0·9%
Eastern Europe and central Asia	0·7 (0·6–0·8)	1 700 000	4·5%
East and southern Africa	6·8 (6·1–7·6)	20 700 000	54·7%
Middle East and north Africa	0·1 (0·1–0·1)	97 000	0·3%
West and central Africa	1·4 (1·1–1·7)	4 900 000	13·0%
Latin America	0·5 (0·3–0·6)	2 100 000	5·6%
Western or central Europe and North America	0·3 (0·2–0·3)	2 200 000	5·8%

Data are from UNAIDS AIDSinfo.