HIV and cancer
Juliet Bennett
Independent Nurse Advisor

Abstract
Despite advances in HIV medicine people living with HIV continue to face many challenges. These include an increased risk of a number of cancers. In order to effectively identify those at risk and meet their healthcare needs nurses need knowledge and vigilance. This will result in appropriate patient education and referral for screening thereby maximising the chances of early detection and enhancing clinical outcomes.

Cancers seen more commonly in people living with HIV will be discussed, including those classified as ‘AIDS defining’ i.e. Kaposi’s sarcoma, non-Hodgkin lymphoma and invasive cervical cancer; in addition to other cancers seen disproportionately in this cohort, namely those of the liver, anus and lung.

Keywords: ART, HIV, cervical, Kaposi’s sarcoma, non-Hodgkin lymphoma, liver, anal, lung

A. Revalidation
This article has been prepared with continuing professional development (CPD) in mind and can be used to support your revalidation. It is estimated that 4 hours of CPD activity will be required for completion of the reading, ‘time out’ activities, the quiz and for writing a brief reflective account in relation to your learning and its applicability to your practice. There is a self-assessment quiz on page XX for you to assess what you have learnt.

B. Aims and intended learning outcomes
The article aims to increase knowledge and confidence in being able to identify risk factors for a range of cancers seen disproportionately in people with HIV; enabling appropriate onwards referral for screening, and improving confidence in the support and care of those who receive an additional cancer diagnosis. After reading this article, undertaking the activities and completing the self-assessment quiz you should:

- have an awareness of the most common cancers seen in people living with HIV, their signs, symptoms and management;
- be able to describe and explain some of the current and key trends in cancer incidence in this population;
- be able to list a range of strategies for prevention, reducing risk and for early detection of these cancers; and
- reflect on, and describe, the extent of your role, and your limitations, as a nurse working in HIV, regarding assessing, educating and referring people living with HIV who may be at risk of the cancers described.

C. Introduction
The Greek physician Hippocrates (460–370 BC), considered the ‘Father of Medicine’, used the terms ‘carcinos’ and ‘carcinoma’ to describe non-ulcer forming and ulcer-forming tumours. In the 19th century Rudolf Virchow, often referred to as the founder of cellular pathology, founded the basis for pathological study of cancers under the microscope and correlated this microscopic pathology to disease manifestations [1].

Cancer pathology
Cancer cells have distinguishing histological features visible under the microscope, for example the nucleus is often large and irregular and the cytoplasm may also display abnormalities. These features are often used as a marker in cancer diagnostics and staging. Different combinations of abnormalities are characteristic of different cancer types.

Carcinogenesis is caused by changes to the regulation of cell division. Mutation of the genetic material of normal cells occurs which, in turn, disrupts the normal balance between proliferation and cell death [2]. The uncontrolled and often rapid proliferation of cells can lead to the formation of benign or malignant tumours. Those tumours that spread to distant locations (i.e. metastasise) and invade other tissues and organs are referred to as ‘malignant’ and can be life-threatening [3].

Causes of carcinogenesis include damage to DNA by exposure to radiation, chemicals, and other environmental sources. Cell mutations can also accumulate naturally over time through uncorrected errors in DNA transcription, making age another risk factor [3]. A number of viruses are known to cause certain types of cancer and genetics are also known to play a role [3]. Stem cell research suggests that an excess of the Sp2 protein may turn stem cells into cancer cells. Furthermore, a fault in the way that antigens react with lymphocytes can impair the function of natural killer cells, ultimately leading to cancer [4].

D. HIV and cancer incidence
Today, in areas when the use of potent antiretroviral therapy (ART) is readily available to people living with HIV, the spectrum of neoplasia seen has changed. The incidence of non-Hodgkin lymphoma (discussed
in Section L) and the skin cancer Kaposi’s sarcoma (discussed in section M) for example, have decreased markedly but there has been a relative increase in tumour types that are collectively referred to as ‘non-AIDS-defining cancers’ (NADCs) [5]. Since 2010 two-thirds of cancers in people living with HIV are estimated to be NADCs. Data on the increased incidence of these cancers in people living with HIV suggest increased incidence for virus-linked cancers such as cervical and anal cancers (caused by human papillomavirus [HPV]), liver cancer (caused by hepatitis B and C) and certain types of lymphoma (associated with Epstein–Barr virus) [6].

A meta-analysis of the incidence of NADCs demonstrated that people living with HIV were twice as likely to develop an NADC as the general population [7]. It is also important to note that people living with HIV are still at risk of the commoner cancers seen in the general population especially in light of changing demographics, for example ageing, see Figure 1 [8,9]. Such demographics also help explain changing rates for the incidence in prostate and lung cancer which are predicted to become the most frequently diagnosed cancers in people living with HIV in developed countries in the next decade. Researchers predict that the incidence rates of all other cancers will either stabilise or decline with the substantial reductions in the incidence of the AIDS-defining cancers, such as Kaposi’s sarcoma, non-Hodgkin lymphoma and cervical cancer, expected to continue [10].

E. Modifiable cancer risks in people living with HIV

According to a US-based 2016 study significantly higher rates of modifiable risks of cancer are found in people living with HIV. These risks include significantly higher levels of smoking, increased alcohol consumption and increased risk of exposure to HPV and hepatitis B and C [11] as listed in Table 1.

A large study of US veterans found the incidence of these cancers was 23% lower in those with long-term viral suppression compared with those with a detectable viral load [12], therefore effective ART with robust adherence is evidently an important factor in reducing risk.

F. HIV and cancer progression

Although people living with HIV may be diagnosed with cancer at an earlier stage because they receive more consistent access to screening and care than the general population, an increase in late cancer diagnosis
CIN 3 – the full thickness of the surface layer is affected. 
CIN 1 – one-third of the thickness of the surface layer 
CIN 2 – two-thirds of the thickness of the surface layer

BHIVA recommend that all patients with HIV and malignancy should be referred to centres that have 
developed expertise in the management of these diseases [14].

G. Cervical cancer

The relationship between HPV infection and cervical cancer is well established and there are two HPV sub-types (HPV16 and HPV18) that contribute up to 70% of cervical cancers. The introduction of the HPV vaccine and screening programmes have provided opportunities to reduce cervical cancer-associated mortality across all cohorts of women including those living with HIV [15]. Currently several vaccines that prevent infection with HPV16 and HPV18 are available. The vaccines can be given as early as at 9 years of age and data report high efficacy for prevention of cervical intraepithelial neoplasia (CIN). An appropriate antibody response to the vaccine is important in establishing long-term immunity. Studies to date, comparing antibody response to the vaccines among women living with HIV, have found the vaccine to be effective and well tolerated [16].

According to BHIVA, 75% of cervical cancer cases in women with HIV are preventable by screening and the organisation currently recommends annual cervical cytology from the age of 25 years; more frequently and earlier where there is clinical concern [14]. For women diagnosed with HIV after the age of 25, particularly those with previous cervical abnormalities or a long interval since their last screening, both colposcopy and cytology should be offered. Screening women living with HIV for CIN may present come challenges, for example access to screening in primary care may be complicated by a reluctance to disclose HIV status. In addition, without the relevant clinical information on a cervical cytology request sample, it may be rejected by the laboratory, or if sampling does not occur within the statutory time frame. Further considerations are outlined in Time out activity 1.

Despite access to effective ART and a significant reduction in the numbers of AIDS defining cancers there has not been a comparable reduction in the incidence of cervical cancer in women living with HIV. Cervical cancer incidence is six-fold greater among women with HIV infection than the general population and it has become a leading cause of death for women in this cohort [17].

On a positive note meta-analysis does show that women with higher nadir CD4 cell counts derive benefit from ART in terms of cervical cancer risk reduction. CIN is graded depending on the depth of the cell changes on surface of the cervix [18]. Compared with women who had low nadir CD4 cell counts they were found to have up to an 80% reduction in the risk for CIN graded 2 or above (see Box 1 for staging and significance) [18]. However HIV is believed to increase incidence of cervical cancer primarily through an increased risk of developing initial precancerous lesions (as a result of impaired clearance of HPV infection). Furthermore ART does not restore HIV-depleted mucosal CD4 cells, which are suspected of potentiating HPV infection and progression [18]. Treatment of cervical precancers in women with HIV infection is associated with increased relapse or unresolved disease, compared with women without HIV [19]. However, these mechanisms would not be expected to affect survival after the cancer develops.

The management of CIN is as per UK guidelines for the general population [14]. Excision of a cone-shaped sample of tissue from the mucous membrane of the cervix may be used either for diagnostic purposes, as part of a biopsy, and/or for therapeutic purposes – to remove pre-cancerous cells [15]. Note that cervical conization can present a risk for subsequent pregnancies ending up in an average preterm birth of approximately 30%, owing to cervical incompetence [21].

There are three main types of surgery for cervical cancer: trachelectomy – the cervix, surrounding tissue and upper part of the vagina are removed; hysterectomy in advanced recurrent disease, and pelvic exenteration. Chemotherapy can be combined with radiotherapy or used as a sole treatment in advanced disease to slow progression and in palliative care. Radiotherapy may also be used alone or in combination with surgical intervention for early stage cancer or combined with...
chemotherapy in advanced disease with a view to controlling symptoms such as bleeding and pain [22].

H. Anal cancer in HIV

The incidence of anal cancer in people living with HIV is up to 40 times higher compared with the general population and it occurs at a much younger age. The highest risk groups are men who have sex with men (MSM) but other men, and women living with HIV women are also at increased risk [14]. Importantly, the incidence of anal cancer appears to have risen with the widespread use of ART [23], although, as mentioned earlier, this may relate to the longer survival of people living with HIV, allowing time for progression of the disease.

The pathogenesis of anal cancer is thought to resemble that of cervical cancer i.e. the disease process is triggered by localised HPV infection leading to intraepithelial neoplasia (AIN), then progression to dysplasia with subsequent risk of invasive cancer. One-third of MSM worldwide are infected with HPV16 [24].

Signs and symptoms include anal bleeding, pain, discomfort, itching, small lumps or ulcers on or inside the anus, anal discharge, a change in bowel habit or bowel control, however, those with AIN often have no symptoms.

**Key point**

The national HPV vaccination programme for MSM began in April 2018. The purpose of the programme is to opportunistically offer the vaccine to MSM up to 45 years of age through specialist sexual health services and/or HIV clinics. To find out more visit the website: www.gov.uk/government/collections/hpv-vaccination-for-men-who-have-sex-with-men-msm-programme

BHIVA recommend that all major HIV units should develop either local clinical expertise and guidelines or referral pathways for suspected anal cancer and precancer. They recommend examination under anaesthetic of the anal canal and rectum with biopsy in all suspected cases. In terms of widespread screening the role of annual anal cytology and anoscopy is not yet proven and consensus on the benefit and applicability of a widespread screening programme has not yet been reached; however, people should be encouraged to check and report any lumps noticed in the anal canal [25].

Where smear testing and cytology is undertaken, as with cervical cytology, the discovery of mildly abnormal cell changes does not necessarily mean the lesions will progress to cancer, however most clinicians recommend treatment options including laser ablation and topical chemotherapy agents. Chemoradiotherapy is used for invasive anal cancer and all treatments yield resolution in the majority of cases although recurrence of lesions is common [24].

I. Head and neck cancers (HNCs)

Cancers in the oral cavity are more commonly seen in people with HIV [26]. HPV is again known to cause a subset of head and neck cancers (HNCs) and associated lesions usually arise in the oropharynx including at the base of the tongue and the tonsils. These HPV-associated cancers are independently associated with sexual behaviour including recent and lifetime number of oral sex partners. In contrast, the majority of unassociated HNCs that occur are primarily associated with tobacco and alcohol use [27], so again people living with HIV are at greater risk as discussed previously.

J. Lung cancer in HIV

Lung cancer is currently the leading cause of cancer-related mortality in people living with HIV. Importantly, the average age of lung cancer onset in the population of people living with HIV is 25–30 years earlier than that of the general population and ART does not appear to have had a significant impact on lung cancer risk, although, a consensus of opinion on this is currently lacking [28]. Most published studies show that HIV infection is a significant independent risk factor for lung cancer but the reasons for the increased incidence in the ART era is unclear. Some possible explanations are described in Section D, including the higher rate of smoking in people living with HIV, however rates of lung cancer in the HIV population adjusted for age are several fold higher than in the general population regardless of smoking status. Some researchers have also identified increased lung cancer risk among people with pre-existing chronic inflammatory lung disease, particularly asthma but these findings have been inconsistent [29].

Lung cancers are divided into two broad types: small cell cancers and non-small cell cancers. The latter are more common and include adenocarcinoma (which frequently metastasise), squamous cell carcinoma and large cell carcinoma. It appears that the incidence of these types of lung cancer is increased in people living with HIV. There is no evidence of an increased incidence of the more aggressive small cell lung cancers in HIV and it is recommended that patients are treated in an identical manner to the population without HIV [14].

**Key point**

The epidermal growth factor receptor (EGFR) is a transmembrane protein that plays a role in epidermal growth. Over activity of this protein is associated with the development of a wide variety of tumours. EGF and its receptor was discovered by Stanley Cohen who was subsequently awarded the Nobel prize for Medicine in 1986 for this discovery [30].
In terms of preventative measures BHIVA emphasise the need to encourage people living with HIV to stop smoking cigarettes and that people should be screened for ‘activating epidermal growth factor receptor (EGFR) mutations’ and treated accordingly. The organisation does not currently suggest a role for screening for lung cancer in people living with HIV [14].

K. Liver cancer in HIV

BHIVA highlights that this is a complex picture ‘because HBV and HCV act as confounding factors’ [14]. The incidence of liver cancer is increasing among people with HIV and hepatitis C (HCV) co-infection mainly amongst those with cirrhosis secondary to this. Interestingly, a large review of current trends showed that while hepatocellular carcinoma (HCC) rates have increased, the incidence of decompensated liver disease or other liver-related deaths in this cohort has declined [31]. The authors of the review also argue that it is perhaps the improved management of liver cirrhosis and HIV treatment that is increasing longevity, which in turn allows viral hepatocarcinogenesis more time to develop into HCC.

HBV is directly carcinogenic and may promote the development of HCC in the absence of cirrhosis [14]. In addition and importantly, HIV affects the natural history of HCV infection in that it increases the likelihood of chronic infection and hastens the development of cirrhosis once chronic infection is established. Other risk factors are given in Box 3.
referred to as ‘high grade’ as the cells appear to be dividing quickly. The risk of developing NHL increases with age and most diagnoses are made in the over 50s age group. These high grade NHL types often respond well to treatment and most people stay in remission for a long time. High grade NHL can be B-cell or T-cell lymphoma and this category also includes Burkitt’s lymphoma. When lymphoma cells are dividing slowly the terms ‘low grade’ or ‘indolent’ are used. Low grade NHLs can develop over a long period of time and some people do not need treatment immediately but are actively monitored until treatment is required [34].

HIV and lymphoma

The most prevalent of the HIV-related lymphomas are diffuse large B-cell non-Hodgkin lymphoma followed by Burkitt’s lymphoma [35]. In the era of effective ART the incidence of NHL has dropped but the incidence of HL has remained stable [36]. NHL is categorised as an AIDS-defining condition however HL is not, although the risk of the latter is markedly increased in those living with HIV, with one meta-analysis showing an 8–10 fold increase, compared with that seen in the general population [37]. The D:A:D research team note that this might suggest risk factors for NHL, and HL may differ in people with HIV [36]. They also found that a lower CD4 cell count boosts chances of both NHL and HL and linked current and historical HIV replication to increased risk, although only for NHL incidence.

Treatment outcome and prognosis has improved significantly over the last two decades with therapy approaches now aimed at complete remission rather than palliation. Treatment options include combination chemotherapy with or without targeted therapy, high-dose chemotherapy and stem cell transplant (for lymphoma that has not responded to treatment or recurrence) and external radiation therapy depending on the tumour site. Both large B Cell and Burkitt’s lymphoma are treatable with chemotherapy and complete remission is possible in the majority of people treated. Relapse – survival without relapse, for a period of 5 years, occurred in approximately 88% of those studied – very similar to rates seen in the general population [38].

M. Kaposi’s sarcoma

Kaposi’s sarcoma (KS) predominantly affects the skin and mucosa, including the oral cavity (in particular the hard palate and gums). It can also affect internal organs such as the lungs and oesophagus. The condition almost always affects those who are immunocompromised such as those taking immunosuppressant drugs post organ transplant or in untreated HIV acquisition, indeed in 1981, early in the AIDS epidemic, it was an extremely high number of cases of an aggressive form of KS in MSM that alerted clinicians to an as yet, unidentified causative agent. In addition those with a genetic vulnerability to the human herpesvirus 8 (HHV-8) are at risk. Infection with HHV-8, otherwise known as KSHV, is responsible for all varieties of KS. Kaposi’s sarcoma has been reported in a number of separate clinical settings, with different presentations, epidemiology and prognoses. All of these occur in the presence of KSHV but with different manifestations in terms of clinical aggressiveness, prognosis and treatment [39].

Key point

Countries bordering the Mediterranean have higher rates of KSHV/HHV-8 infection than the rest of Europe. Classic KS usually affects older men from this region. It causes purplish skin lesions, usually on the feet. This form of KS tends to be a chronic condition that progresses slowly [40].

In people living with HIV, KS is an AIDS-defining condition which typically presents with skin or mucosal red or purple macules, see Figure 2, and these tend to progress rapidly to raised plaques. The lesions can be singular or multiple and tend to occur on the head
and neck, back, abdomen and mucous membranes. In more advanced cases, they can be found in the stomach and intestines, the lymph nodes and the lungs.

In Mediterranean populations where classic KS is seen, and in sub-Saharan Africa, where KS occurs in children, vertical transmission of KSHV through saliva is considered to be the most likely route of transmission, for example where mothers pre-chew food for their infants. The virus is also highly prevalent in MSM and more so in MSM who also have HIV, where the risk for transmission is associated with the number of sexual partners. Again it is considered likely that the most probable route of transmission is also through saliva. In Africa, since the spread of HIV, epidemic KS has become more common in both sexes [41].

In terms of prevention currently there is no vaccine against HHV-8. In theory specific therapies against KSHV may be beneficial but published retrospective cohort studies to date are contradictory. ART is effective in preventing tumour formation, resulting also in significant reductions in the levels of the causative herpes virus in the oropharynx. Other antiviral drugs such as valaciclovir and famciclovir have only a modest effect [14].

Diagnosis of KS is usually based on the visual appearance of lesions but BHIVA recommend that diagnosis should be confirmed histologically. Lesions are graded into patch, plaque or nodular grade disease. Because visceral disease is uncommon, screening with CT scans, bronchoscopy and endoscopy etc. are not advised unless the individual is symptomatic. Treatment, alongside ART, can be radiotherapy or intralesional vinblastine with systemic chemotherapy used in more advanced cases [14].

N. Role of the nurse

Nurses have the clinical knowledge, the communication skills and holistic overview of the individuals in their care and are, therefore, well placed to assist the multidisciplinary team in identifying, assessing and referring those at increased risk of the range of the cancers discussed in this article. High-quality nursing care requires vigilance so being aware of the risk factors and signs and symptoms for a range of cancers seen more frequently in people living with HIV is a priority aspect of care. Robust assessment and referral processes need to be embedded in nursing practice. There is also a clear educational role for nurses in supporting lifestyle changes that will reduce the impact of modifiable risk factors, in particular in facilitating smoking cessation. Motivational interviewing techniques can support behavioural change, referring for smoking cessation counselling and prescribing nicotine replacement medication (a combined approach is deemed more effective) are all aspects of the nurse’s role. In addition, reiterating the benefits of cessation with repeated clear and strong message reinforcement alongside personalised advice and goal setting is also helpful.

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P. References

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Correspondence: Juliet Bennett
jvjbennett@yahoo.com