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Malignancy in HIV infection is thought to result from a decrease in immune surveillance, an imbalance between cellular proliferation and differentiation, and persistent antigenic stimulation by HIV itself and by other oncogenic viruses. Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL) and carcinoma of the cervix are all AIDS-defining conditions. Hodgkin's lymphoma, lung and anal carcinomas all occur at increased frequency in those with HIV infection although they are not classified as AIDS-defining conditions.

The spectrum and incidence of malignancies has changed since the introduction of combination antiretroviral therapy (cART) and improvements in prophylaxis and management of opportunistic infections. In general, therapeutic strategies for malignancies in people with HIV are the same as for those without immunosuppression. However, toxicity is often more significant.

## 17.1 Non-Hodgkin's lymphoma

### 17.1.1 Epidemiology

The risk of developing NHL is dramatically increased in people with HIV infection, with a 134-fold increased incidence above that seen in the general population.<sup>1,2</sup> Histologically, AIDS-related NHL (AIDS-NHL) is B cell-derived and is characterised by cellular pleomorphism and diffuse growth patterns. Approximately 70% of AIDS-NHL are systemic (as opposed to primary central nervous system NHL or primary central nervous system lymphoma (PCNSL)). They are predominantly of the Burkitt's or Burkitt-like lymphoma type (also termed small non-cleaved-cell lymphoma), and the diffuse large B-cell lymphoma type. About 30% of AIDS-NHL are PCNSL, the majority of which are diffuse large B-cell lymphomas.<sup>3</sup> Two additional forms of lymphoma which are nested within the systemic NHL grouping have been described in association with HIV infection. Primary effusion lymphoma, also termed body-cavity-based lymphoma; and a specific form of diffuse large B cell lymphoma involving the oral cavity, termed plasmablastic lymphoma. Primary effusion lymphoma is a lymphoma of the serous membranes which produces lymphomatous effusions without exhibiting significant bulk tumour growth.<sup>4</sup> Other types of NHL, such as low-grade B and T cell NHLs may occur sporadically in the context of HIV infection, but these are not considered to be HIV-related.<sup>1</sup> The incidence of AIDS-NHL has changed since the introduction of potent antiretroviral therapy, with a significant decrease in the incidence of PCNSL and a smaller decrease in diffuse large B cell lymphoma; however, small non-cleaved-cell NHL has shown no decline.<sup>5-7</sup>

Since the widespread use of cART, the prognosis of HIV-NHL has improved with better tolerance of chemotherapy and better

response rates. Both the rate of complete remission and the duration of complete remission have increased. The treatment-related deaths due to complications of HIV are also declining.<sup>8,9</sup>

### 17.1.2 Aetiology

Although AIDS-NHL occurs in association with HIV and the Epstein Barr virus (EBV), there is no proven causal relationship between HIV replication and NHL. In the context of EBV-associated NHL, HIV causes lymphoid hyperplasia accompanied by a reactivation of EBV infection which gives rise to the production of polyclonal, immortalised B cells. These activated B cells may then accumulate chromosome abnormalities and rearrangements during repeated cycles of replication.<sup>1</sup> This is thought to occur because of lack of specific anti-EBV CD4 cell function as a direct result of HIV affecting quality and function of the CD4 cells.<sup>10</sup> EBV genes are incorporated in 100% of PCNSL in people with HIV infection and detection of EBV by PCR may provide an important tool assisting diagnosis. EBV is always associated with the endemic form of Burkitt's lymphoma, but is not consistently present in Burkitt's-like NHL (small non-cleaved-cell lymphomas). Plasmablastic lymphoma also has a strong association with EBV, distinguishing it from plasmacytomas, with which it is frequently histologically confused.<sup>5</sup> Primary effusion lymphoma is causally related to co-infection with human herpes virus 8 (HHV8) and HIV.<sup>11</sup>

### 17.1.3 Clinical presentation

The clinical presentation of AIDS-NHL varies according to the histological type. In systemic AIDS-NHL, the small non-cleaved-cell type presents at a higher CD4 cell count (median 150 cells/ $\mu$ L) compared with the diffuse large B cell lymphoma, which occurs at more advanced levels of immunosuppression (median CD4 cell count 50 cells/ $\mu$ L). Extranodal involvement occurs in the vast majority of AIDS-NHL (75-90%),<sup>1,12</sup> with the most frequently involved sites being bone marrow, gastrointestinal tract, meninges and liver. The common finding of B-symptoms (fever, night sweats and weight loss exceeding 10% of body weight in six months) may lead the clinician to suspect an opportunistic infection, therefore delaying diagnosis.<sup>1</sup>

### 17.1.4 Investigations

Patients with asymmetrical or rapidly progressive lymph node enlargement (with or without constitutional B-symptoms) should preferably undergo excisional lymph node biopsy. Fine-needle aspirates and core biopsies often do not provide adequate samples for histological evaluation and diagnosis. Immunophenotyping should be performed on the biopsy to aid the plan for treatment. This is particularly important given the increasing number of monoclonal antibody adjunctive treatments now available. For instance, CD20 positivity mandates consideration of the use of rituximab (monoclonal

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anti-CD20) in each case, although the risks of treatment need to be weighed up against the benefits for each patient.<sup>13</sup>

Staging evaluations to be performed include:

- computed tomography (CT) scans of the abdomen, pelvis and thorax
- positron emission tomography (PET)
- CT scan or magnetic resonance imaging (MRI) of the brain
- bone marrow biopsy with aspirate and trephine for histopathology, immunophenotyping, gene rearrangement studies and to exclude any infective cause for symptoms
- lumbar puncture for cerebrospinal fluid analysis: biochemistry, microscopy and culture, cytopathology and flow cytometry. At least 5 mL should be sent allowing for the adequate exclusion of central nervous system (CNS) disease and for special tests including EBV DNA polymerase chain reaction.

Approximately 30% of people will have bone marrow involvement and 10-20% will have leptomeningeal involvement.

Baseline estimations of left ventricular function (ultrasound or nuclear medicine) should be considered in all patients. The risk of cardiac disease must be assessed with extra caution if an anthracycline is to be used in the chemotherapy regimen.

### 17.1.5 Management

Assessment of tumour burden includes serum lactic dehydrogenase and uric acid levels.

In patients with systemic AIDS-NHL, combination chemotherapy is the standard. However, in patients with substantial tumour bulk, radiotherapy may be used in addition to chemotherapy. A number of chemotherapy regimens have been tried in AIDS-NHL, including standard and modified CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), M-BACOD (methotrexate with folinic acid rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone) and infusional CDE (cyclophosphamide, doxorubicin and etoposide).

Results from chemotherapy have previously been poor, because treatment has been complicated by toxicity, due in part to substantial bone marrow involvement in many patients and advanced immunosuppression.<sup>14</sup> More recently, infusional regimens such as CDE or EPOCH (etoposide, prednisolone, oncovin (vincristine), cyclophosphamide and hydroxydaunorubicin [doxorubicin/adriamycin]) have been associated with superior results compared with standard dose CHOP chemotherapy. The role for dose-dense treatment (every 10 to 14 days instead of the usual 21 days standard dose therapy in HIV-NHL) awaits full evaluation. The addition of rituximab to CHOP chemotherapy (R-CHOP) has been the subject of three small studies. There has been some benefit shown in selected studies but no case for the routine use of rituximab can yet be made given the increased risk of opportunistic infection complicating its use.<sup>15,16</sup> The addition of rituximab to the infusional regimens is also showing promising results particularly with granulocyte colony stimulating factor support.<sup>8</sup>

There is limited information regarding autologous or homologous bone marrow transplantation in patients with HIV and relapsed or refractory NHL. Most data pertain to autologous bone marrow transplantation (ABMT). In small series, stem cell collection capacity and toxicity of treatment were similar to

that of ABMT in those without HIV infection; however numbers and experience are limited.<sup>17,18</sup> ABMT should be considered if HIV is well controlled, and the lymphoma disease is refractory to standard treatments but remains chemosensitive. It should only be considered, performed and managed by a specialist unit experienced in transplantation.

Patients with CD4 cell counts greater than 100 cells/ $\mu$ L have remission rates of up to 94% and median survival exceeding 23 months when treated with combination chemotherapy.<sup>19</sup> Some factors associated with a poor prognosis include: CD4 cell count below 100 cells/ $\mu$ L; prior AIDS-defining illness; age greater than 35 years; intravenous drug use; and low performance status (Karnofsky performance score less than 70).<sup>14</sup> Referral of all cases of AIDS-NHL to a medical oncologist experienced in the current management of HIV-associated malignancies is strongly recommended. The addition of cART to chemotherapy is associated with an improved outcome.

## 17.2 Primary central nervous system lymphoma

### 17.2.1 Clinical presentation

Patients diagnosed with PCNSL have usually been diagnosed with an AIDS-defining condition and are typically profoundly immunosuppressed (CD4 cell count <50 cells/ $\mu$ L).<sup>20,21</sup> Many cases of PCNSL are diagnosed at autopsy.<sup>12</sup> The most common features at clinical presentation are headache, nausea, lethargy and fatigue, personality changes, and focal neurological deficits. Seizures may occur in up to a third of patients. Fever is rare, and the onset of symptoms occurs over several weeks.

### 17.2.2 Investigations

Characteristic changes shown on a brain CT or MRI scan include the presence of a single lesion with diffuse enhancement after administration of contrast, and surrounding oedema.<sup>21</sup> The lesions are commonly periventricular in location, but can be found in the cerebrum, cerebellum, basal ganglia and brainstem.<sup>22</sup> Unfortunately, radiological findings may not always discriminate between lesions caused by primary CNS lymphoma and lesions caused by other processes such as toxoplasmosis. Failure to respond to toxoplasmosis therapy should raise the possibility of PCNSL. Brain biopsy usually establishes the diagnosis but may also cause significant morbidity and mortality. Lumbar puncture should be considered because malignant cells are demonstrated in 10-20% of patients. The detection of EBV-DNA by PCR in the cerebrospinal fluid occurs in over 75% of patients presenting with PCNSL and may obviate the need for a formal brain biopsy.<sup>12</sup>

### 17.2.3 Management

Although PCNSL is extremely sensitive to radiotherapy, treatment outcome has, until recently, been extremely poor, with early studies showing a median survival of 72 days.<sup>21</sup> The incidence of PCNSL has decreased and the overall survival improved since the widespread use of cART.<sup>13</sup> The lack of CD4-specific EBV immunity is associated with an increased risk of developing PCNSL.<sup>10</sup> Recently, the addition of (usually adjuvant CHOP) chemotherapy to radiotherapy has been associated with improvements in response rate and survival, and improvements in immune status induced by potent antiretroviral therapy.

High-dose methotrexate is reported to have similar response rates to radiotherapy and standard dose chemotherapy, although good comparative studies have yet to be done in the HIV population.<sup>23</sup>

## 17.2.4 Primary effusion lymphoma

Primary effusion lymphoma is uncommon, accounting for less than 3% of AIDS-NHL.<sup>12</sup> It presents as lymphomatous effusions arising in serous cavities (pleural, pericardial and peritoneal), without a tumour mass. It is a high grade B cell NHL associated with HHV8 infection. In a cohort of 28 patients, a poor performance status and no treatment with cART were poor prognostic factors. In this group, 50% achieved a complete remission in response to chemotherapy<sup>24</sup> and 32% were alive at four years.<sup>20,25</sup> This remains a rare but serious complication of HIV infection.

## 17.3 Hodgkin's disease

### 17.3.1 Epidemiology

Hodgkin's disease (HD) is the most common non AIDS-defining cancer to occur in people with HIV infection. The relative risk of HD in this group is about 13 times the risk in the general population.<sup>26-28</sup> The risk of HD has increased in the post-cART era. It is the only malignancy thus far to be reported as such.<sup>28</sup> Studies have shown that HD occurs at increasing frequency with advancing immunosuppression, with the relative risk of developing HD being greatest in the six months prior to, and three months after, a diagnosis of an AIDS-defining illness.<sup>24,27</sup>

### 17.3.2 Clinical features and treatment options

The clinical presentation and pathological features of HD in people with HIV infection are markedly different to that of HD in the general population<sup>29-31</sup> (Table 17.1).

Response to therapy for HD in people with HIV infection was poor in the pre-cART era.<sup>1</sup> In the post-cART era, the rates of response and duration of response to treatment approached those of HD in the general population. The optimum therapy includes radiotherapy and/or chemotherapy. The chemotherapy regimen is usually ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) or a MOPP (mechlorethamine, oncovin, procarbazine, prednisolone) variant.<sup>32</sup> Radiotherapy to bulky disease or early stage disease contributes significantly to ideal disease control.

Significant drug toxicity may be seen in people with HIV infection with HD. Dose reductions are often required because of neutropenia and thrombocytopenia and other more specific HIV-related phenomena such as neuropathy or opportunistic infections such as cytomegalovirus disease.<sup>33</sup> Recently, the use of Stanford V regimen (a 12-week course of doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide,

and prednisolone, and adjuvant radiotherapy in combination with cART) has been used in HD in patients with HIV infection.<sup>34</sup> The Stanford V regimen was associated with less toxicity than other treatment strategies, and 55% of patients did not require any dose reduction of chemotherapy or delay in chemotherapy cycles.

## 17.4 Cervical cancer

### 17.4.1 Epidemiology

Invasive cervical cancer has been included among AIDS-defining conditions since 1993. There is now evidence of an increased incidence of invasive cervical cancer as a consequence of HIV infection. Studies from Europe have shown significant increases in rates of invasive cervical cancer<sup>26,35</sup> as have other studies from both the USA and Africa.<sup>36-40</sup> Decreased survival early in the epidemic may have masked the risk for invasive cervical cancer in data used from this period, while late diagnosis of HIV may negate the potential gains from the increased cervical screening recommended in this group.<sup>41</sup> In one of the US studies to show an increased risk of invasive cervical cancer, the diagnosis of cervical cancer preceded the diagnosis of HIV infection and was the trigger for HIV screening in 71% of cases.<sup>42</sup> The mode of HIV transmission also appears to influence risk, with injecting drug users having three times the rate of invasive cervical cancer compared to those who contracted the infection by heterosexual contact.<sup>35,43</sup> It has been suggested that the increased incidence of invasive cervical cancer in this group may reflect a component of immunosuppression induced by injecting drug use,<sup>44</sup> but epidemiological studies have not shown an increased risk in HIV-negative injecting drug users.<sup>35</sup> A more likely explanation is a behavioural one, whereby such activities as sex work may expose people to frequent human papilloma virus (HPV) infections, and more infrequent use of cervical screening programs by women who are injecting drug users with HIV infection than other women with HIV infection.<sup>45</sup> Recent work from Nigeria demonstrates that the prevalence of cervical dysplasia in women who contracted HIV heterosexually is high at 10.9% versus 2.6% in an HIV-negative control group.<sup>46</sup> This finding supports the screening and active intervention programs in women with HIV, to detect the disease at an early stage when therapy is effective.

### 17.4.2 Clinical features and management

There are few studies evaluating the clinical presentation and prognosis of invasive cervical cancer in populations with HIV. Information has come predominantly from case series which lacked HIV-negative control groups. Women in these studies tended to present with more advanced cervical

Table 17.1 Differences in clinical presentation of Hodgkin's disease in people with HIV and without HIV<sup>29-31</sup>

	With HIV infection	Without HIV infection
Unfavourable histological subtypes (mixed cellularity and lymphocyte depletion)	70%	Rare
Median age at presentation (years)	29	38
B-symptoms at presentation	77%	35%
Extranodal disease	Common (bone marrow, liver, spleen) 63%	Uncommon 29%
Non-contiguous tumour spread	60%	Rare
Mediastinal adenopathy	13%	71%

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cancer, frequently with metastases at unusual sites at the time of diagnosis.<sup>45</sup> They experienced high recurrence rates after standard treatment (88% at one year) and a high death rate.<sup>42</sup> Invasive cervical cancer was not associated with advanced immunosuppression; the mean CD4 cell count at diagnosis was 312 cells/ $\mu$ L, and cervical cancer was the AIDS-defining illness in 93% of the patients.<sup>42</sup> In two studies, women with HIV were younger than HIV-negative women at the time of invasive cervical cancer diagnosis and they had a poorer response to therapy.<sup>45-47</sup>

Surgical excision is the standard of care for early invasive cervical cancer, but, as many women with HIV present with advanced disease, this option is rarely adequate. For more advanced disease, consideration should be given to the same therapy options currently offered to HIV-negative women: that is, radiation combined with chemotherapy.<sup>40</sup> The prognosis for women with HIV appears poor, with invasive cervical cancer being the cause of death in 95% of women with both diagnoses.<sup>42</sup>

### 17.4.3 Screening

Although the association between increased rates of cervical dysplasia and cervical intraepithelial neoplasia (CIN) and HIV is clear, the effect of HIV on the development and progression of these precursor lesions to invasive cervical cancer is complex and incompletely understood. HPV infection appears to be critical to the development of CIN, while HIV influences both the susceptibility to, and nature of HPV infection. Women with HIV are also likely to be infected with oncogenic HPV subtypes, multiple subtypes and to demonstrate persistent HPV infection.<sup>48-50</sup> Additionally, CIN in women with HIV is likely to involve multiple sites, and have high rates of recurrence and rapid progression after standard therapy.<sup>51</sup> Given these findings, cervical screening programs advocate more frequent Pap smears in women with HIV than in HIV-negative women. Current clinical guidelines for women with HIV recommend annual Pap smears after two successive normal smears six months apart.<sup>41</sup> However, screening cervical cytology in women with HIV has been called into question, as a number of studies show histologically-proven dysplasia despite normal cervical cytology in 18-30% of cases.<sup>52,53</sup>

A vaccine against HPV 6, 11, 16 and 18 has been licensed. The safety and efficacy of these vaccines in preventing new infection with oncogenic subtypes, or in boosting immunity to current infection with one of the oncogenic subtypes in HPV/HIV co-infection needs to be investigated. The benefits of an assiduous screening program should also be studied.<sup>54</sup>

Given the potential problems with screening, as well as the often extensive and multisite dysplastic involvement and the rapid progression of these lesions in a young population, another approach is semi-annual screening with colposcopy. The use of adjunctive 5-fluorouracil combined with standard excisional/ablative therapy was shown in a randomised trial to lead to fewer recurrences of CIN, a longer time to recurrence and a lower grade of dysplasia at recurrence.<sup>55</sup>

## 17.5 Anal cancer

### 17.5.1 Epidemiology

The first case of anal cancer in a patient with HIV was reported in 1989,<sup>56</sup> and the first case series followed soon after.<sup>57</sup> Anal

cancer in the period before 1970 was a rare malignancy with a reported incidence of 0.7 per 100 000 in males and slightly more in females (0.9 per 100 000).<sup>58</sup> Dramatic changes have been observed in these rates in the general population, with incidence rates in males having risen to 1.2 per 100 000 and in females to 1.3 per 100 000 between 1995 and 1999.<sup>59</sup> The reasons for the increase are not entirely clear. However, there is speculation that increased rates of infection with oncogenic HPV subtypes associated with the development of anal cancer (e.g. HPV 16) may have occurred over the same period.<sup>60</sup> Homosexual men with a history of receptive anal intercourse and men with HIV regardless of transmission category are at additional increased risk of anal cancer compared with the general population, with the highest rates seen in homosexual men with HIV. The relative risk of anal cancer in men with HIV increases as HIV disease progresses, from 13.9 in the two to five years before AIDS, to 27.4 in the two years prior to AIDS, and 84.1 at or after an AIDS diagnosis.<sup>61</sup>

### 17.5.2 Aetiology

It is thought that anal dysplasia represents the precursor lesion for anal cancer. Anal dysplasia and squamous intraepithelial lesions (SIL) or anal intraepithelial neoplasia (AIN) are described variously by different groups. In the AIN nomenclature, lesions are described using a similar staging system to that in CIN, whereas in the SIL nomenclature, lesions are described in terms of low-grade SIL (equivalent to CIN I/II) and high-grade SIL (equivalent to CIN III/IV). As with cervical dysplasia, many low-grade SIL will regress, whereas few high-grade SIL regress. However, in contrast to cancer of the cervix, the time to development of anal cancer after development of high-grade SIL is not currently known. Studies looking at the rate of anal dysplasia in men and women with HIV have shown remarkably high rates in these groups. Rates of up to 65% have been detected in homosexual men with HIV,<sup>62</sup> while 26% of women with HIV and 8% of HIV-negative women had some grade of anal SIL.<sup>63</sup> HPV subtype appears to cause different histopathological severity, with HPV type 16 almost exclusively associated with high-grade SIL and anal cancer, while HPV types 6 and 11 are associated with low-grade SIL.<sup>60</sup> The list of viral subtypes has been expanded, and subtypes are now classified into two groups: group A, associated with low-grade SIL (HPV subtypes 6/11/42/43/44); and group B, associated with high-grade SIL (HPV subtypes 16/18/31/33/35/39/45/51/52/56/58).<sup>64</sup> As with cervical dysplasia in women, infection with multiple HPV subtypes is more common in men with HIV than HIV-negative men (73% versus 23%), and infection with group B HPV subtypes is seen more commonly in those with advanced HIV disease.<sup>64</sup>

### 17.5.3 Management

The management of these lesions once detected is to remove them if possible and then perform regular anal mapping which consists of a formal series of biopsies to exclude invasive disease every 6 to 12 months. Topical fluorouracil may relieve symptoms but has not been demonstrated to reduce the rate of progression from *in situ* to invasive disease.<sup>65</sup>

Anal cancer is highly sensitive to the effects of both chemotherapy and radiation. In treated patients, survival at five years in the general population is 80%. Combined chemotherapy and radiation with 5-fluorouracil and mitomycin

C has become the standard therapy because sphincter function can be maintained in the majority of patients.<sup>66</sup> Until recently, it was thought that therapy-related toxicities (haematological, skin and gastrointestinal) were increased in people with HIV infection, and that dose reductions were often required.<sup>67</sup> However, recent studies have shown that increased risk of toxicity with severe mucositis is related to CD4 cell count and is usually only severe in patients with pre-treatment CD4 cell counts of less than 200 cells/ $\mu$ L.<sup>68</sup> In the post-cART era the outcomes for HIV patients have approached that of HIV-negative patients. In the largest reported series of 32 patients, the five-year, cancer-free survival was 75% after sphincter-preserving chemo-radiotherapy: close to the 80% survival reported in an HIV-negative series. Overall survival was predictably associated with a higher CD4 cell count and lower HIV viral load.<sup>69</sup>

### 17.5.4 Screening

Anal cytology has become the most common method for detection of anal dysplasia; however, anal cytology does not always correspond to histological stage, and a low threshold for biopsy to determine the grade of dysplasia has been recommended.<sup>70</sup>

Given the high rates of anal cancer and anal dysplasia, some advocates have recommended that screening programs, similar to those for cancer of the cervix in women, be undertaken in those with HIV.<sup>71</sup> Although screening may detect early anal cancers, the impact of such screening programs on the development of anal cancer is not clear. In contrast to the situation with cervical cancer, the treatment of SIL has yet to be shown to decrease either SIL or the later development of anal cancer. In one recent study, 23 of 29 patients treated surgically by either excision or cauterisation had persistence of anal SIL or recurrence in less than one year.<sup>72</sup>

Initial studies demonstrated minimal impact of antiretroviral therapy on either anal SIL or HPV infection; however, these studies only examined the first six months after initiation of therapy.<sup>71,73</sup> Regression or decreased development of anal dysplasia and an increased clearance of HPV infection may become evident with longer follow-up.

## 17.6 Lung cancer

### 17.6.1 Epidemiology

The relationship between HIV and the risk of development of lung cancer remains controversial, as the epidemiological data are both conflicting and inconclusive.<sup>74</sup>

Studies using data from early in the HIV/AIDS epidemic, prior to the widespread use of prophylaxis for opportunistic infections and the use of antiretroviral therapy, were not able to distinguish any increased risk of lung cancer because most patients did not survive long enough for lung cancer to develop or be diagnosed. One of the largest studies conducted to date linked HIV/AIDS and cancer registry data from both early and late in the HIV epidemic, and involved 302 834 people. This recent study has suggested that lung cancer occurs more frequently in the setting of HIV-related immunosuppression compared to the general population, with a relative risk of 4.5,<sup>24</sup> but this risk declined between 1990 and 2002 with the relative risk changing from 3.3 to 2.6 in this time period.<sup>28</sup>

It is currently not clear whether this excess rate of lung cancer is related solely to immunosuppression or whether other contributing factors, such as higher rates of tobacco consumption or chronic respiratory infections, are also involved. Few epidemiological studies using linkage data have been able to include smoking rates in the analysis, as this information is not recorded in the databases. By assuming a smoking rate of 100% in their HIV cohort, and comparing this to the expected rate of lung cancer in male smokers in the corresponding age group, Parker et al. were able to demonstrate that the rate of lung cancer in the HIV cohort was greater than could be explained by smoking alone.<sup>74</sup>

### 17.6.2 Clinical features and management

Lung cancer in people with HIV differs both clinically and pathologically from that which occurs in the general population.<sup>5</sup> People with HIV are generally younger at the time of diagnosis of primary lung cancer, with a median age between 38 and 49 years,<sup>74,75</sup> compared with the median age of 68 years in the general population.<sup>76</sup> The median CD4 cell count at diagnosis ranges from 150 to 230 cells/ $\mu$ L.<sup>75,77</sup> Although all histological subtypes may be seen in patients with HIV infection, adenocarcinoma predominates (occurring in 48% of patients), while only 13% have small cell carcinoma.<sup>78</sup> The prognosis for people with HIV diagnosed with primary lung cancers tends to be poor, with a median survival of four to 20 weeks,<sup>75,79</sup> and a one-year survival rate of 0-10%.<sup>80,81</sup> The reason for this markedly decreased survival in comparison with other populations is not clear. Although opportunistic infections have been described in patients with HIV with lung cancer treated with chemotherapy, three-quarters of patients die from lung cancer itself rather than a secondary disease.<sup>75</sup>

## 17.7 Other cancers

As people with HIV are living longer, other neoplasms such as skin cancers, renal cancer, testicular cancer and lip cancer are occurring at increasing rates.<sup>82</sup>

Increased incidences of skin neoplasms including basal cell carcinoma, squamous cell carcinoma<sup>83</sup> and melanomas have been reported in people with HIV.<sup>84</sup> Basal cell carcinomas occur at a younger age in this group, with 54% of cases occurring in patients with HIV aged less than 40 years compared with only 5% of this age group in the general population. In people with HIV infection, basal cell carcinomas are more likely to occur on the trunk, with only 29% occurring on the head and neck area, in comparison with 85% in the general population.<sup>83</sup> Squamous cell carcinomas also occur at a younger age in people with HIV, and behave more aggressively. Recurrence occurs in up to 20% of cases following therapy and there is a tendency to early metastasis in patients with HIV.<sup>84</sup> With these unfavourable characteristics, it is important to refer any suspicious lesions for prompt assessment and biopsy. Although there is an increased risk of its occurrence in other forms of immunosuppression,<sup>85</sup> malignant melanoma remains a rare cancer in people with HIV infection.<sup>86</sup>

Data from the US Multicenter AIDS Cohort Study indicate that there is a significant increase in the incidence of testicular cancer (standardised incidence rate 3.9) in homosexual men with HIV,<sup>87</sup> but the natural history of this malignancy, as well as cure and survival rates, are similar to those in the general

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population.<sup>5,33</sup> Increased rates of lip cancer in people with HIV have been noted in Australia.<sup>88</sup> However, no clinical series has yet been reported, so the natural history of this malignancy in HIV infection is unknown.

### 17.8 Castleman's disease

Multicentric Castleman's disease is a specific type of lymphoproliferative disorder usually characterised by persistent slowly progressive lymphadenopathy. In the general patient population, the disease usually progresses slowly and has not been regarded as a malignancy given it is polyclonal in origin and may exist for years or decades without requiring treatment. In patients with HIV, the situation is usually markedly different: the disease may progress quickly and require treatment similar to lymphoma. Steroids generally control fever but bulky disease requires other chemotherapeutic agents.

The histological picture in lymph nodes is of angiofollicular hyperplasia and plasma cell infiltration, forming sheets of cells in the mantle and the interfollicular zone of lymphoid organs. These plasmablastic cells are derived from naïve B cells and are polyclonal, rather than monoclonal, in origin.<sup>89</sup> Castleman's disease shows a strong association with HHV8, which is demonstrated in 100% of patients with HIV who develop this condition.<sup>90,91</sup> HIV patients tend to present with multicentric Castleman's disease as opposed to general patients who tend to present in a unicentric fashion. The two main histological variants (hyaline vascular and plasma cell as described above) are also represented differently in the HIV population.

Increased rates of malignancies associated with HHV8, such as KS, NHL and primary effusion lymphoma, have also been noted in patients with HIV with multicentric Castleman's disease.<sup>82</sup>

The clinical features include constitutional symptoms of fever, fatigue and weight loss, with splenomegaly and peripheral lymphadenopathy.<sup>92</sup> There may be a cyclical nature to the symptoms, at least initially. Table 17.2 indicates common signs and symptoms. Diagnosis is made by a lymph node biopsy, which shows changes characteristic of hyalinised germinal centres, vascular hyperplasia and plasma cell infiltrates.<sup>92</sup>

A number of therapeutic interventions have been tried in patients with HIV and multicentric Castleman's disease, including corticosteroids, chemotherapy, chemotherapy plus corticosteroids and splenectomy.<sup>92,93</sup> There have been two case reports describing durable remissions using oral etoposide.<sup>94</sup> Most descriptions of therapy of multicentric Castleman's disease in the setting of HIV infection are isolated case reports and small case series. More recently the use of rituximab (humanised monoclonal anti-CD20) has been reported with some degree of success, however, given the persistent B cell lymphopenia that usually persists after administration, this drug should be carefully considered as an option in each patient individually. The evidence for its use is the subject of only small case series, but is gaining worldwide acceptance.<sup>95</sup>

Therapy tends to lead to a rapid but short-lived clinical response, with disease progression in most patients. Ongoing corticosteroids may control symptoms well and the dose should be maintained at a minimum to control fever and other systemic symptoms. Mortality is high, with 40% of those with Castleman's disease dying within 12 months of diagnosis.<sup>92</sup> Resolution of multicentric Castleman's disease following cART has been described,<sup>96</sup> however, other investigators have described no

Table 17.2 Clinical presentation of multicentric Castleman's disease

Symptom/sign	Frequency of symptom at presentation (%)
Fever	100
Splenomegaly	100
Peripheral lymphadenopathy	90
Hepatomegaly	70
Severe weight loss	70
Respiratory symptoms	65
Oedema	55
Pleural effusion	20
Arthralgia	10
Microcytic anaemia	80
Thrombocytopenia	80
Leukopenia	35
Reduced albumin	50
Increased alkaline phosphatase	30

Adapted from: Oksenhendler E, Duarte M, Soulier J, et al. Multicentric Castleman's disease in HIV infection: a clinical and pathological study of 20 patients. *AIDS* 1996;10:61-7.

effect of cART on multicentric Castleman's disease.<sup>93</sup> Attempts to use HHV8-specific antivirals have also been unsuccessful. A particularly aggressive form of multicentric Castleman's disease has been described in patients soon after initiation of cART, probably representing a form of immune reconstitution disease.<sup>97</sup>

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