British HIV Association guidelines for HIV-associated malignancies 2013

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Version 1
25 July 2013

1.0 Introduction

1.1 Introduction

HIV infection is associated with three AIDS-defining malignancies (Kaposi sarcoma, high grade B-cell non-Hodgkin's lymphoma and invasive cervical cancer) as well as an increased risk of many other malignancies. The clinical care of patients with these tumours requires a multidisciplinary approach drawing on the skills and experience of all healthcare professional groups. Moreover, optimal care can only be achieved by the close co-operation of oncologists, haematologists and HIV physicians, and unless all these clinicians are intimately involved in the care of patients it is likely that the outcome will be less favourable. Patients with HIV-associated malignancies should therefore only be managed in a centre dealing with large numbers of patients with these tumours.

The minimum number of patients that an HIV oncology service should manage has not been defined. Several studies and a Cochrane review have shown that the more HIV patients treated by a centre, the better the outcomes [1-3]. Similarly, Improving outcomes in haematological cancer published by NICE in 2003 included a systematic review of published evidence suggesting that higher patient volumes are associated with improved outcomes and that outcomes in specialist centres are better. They advocated that all patients with haematological cancer should be managed by a multidisciplinary haemato-oncology team serving a population of at least 500,000 [4]. An audit study in North London confirmed the better management of patients with AIDS-related lymphomas in HIV centres with cohorts of >500 patients (level of evidence tbc [III?]) [5] and an audit in Canada also showed that clinicians treating larger numbers of patients with AIDS-related lymphoma provided better care [6]. An additional benefit of centralisation could be greater uptake of HIV testing amongst patients diagnosed with cancers including lymphomas as advocated in BHIVA testing guidelines [7] and in the US [8]. This remains a concern since UK lymphoma clinicians are often overly reluctant to adopt universal testing [9] and uptake remains low even for AIDS-defining malignancies [10].

We recommend that all patients with HIV and malignancy should be referred to centres that have developed expertise in the management of these diseases (level of evidence 1B). The multidisciplinary medical team managing these patients must include HIV physicians, oncologists, haematologists and palliative care physicians. In line with national cancer waiting times, all patients with suspected cancers must be referred urgently and seen within 2 weeks of referral. Moreover, the NHS Cancer Plan sets out the goal that no patient should wait longer than 1 month from an urgent referral with suspected cancer, to the start of treatment. A survey of 190 attendees at the Annual 2013 BHIVA Conference found that clinicians, community representatives and users felt that experience in managing HIV-related malignancies was of greatest

importance in determining patient pathways and that a minimum of 50 patients per year should be required for service designation (level of evidence 2D).

1.2 Key recommendations

We recommend that all patients with HIV and malignancy should be referred to centres that have developed expertise in the management of these diseases (level of evidence 1B).

We suggest that a minimum of 50 patients per year should be required for service designation (level of evidence 2D).

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2.0 Kaposi sarcoma (KS)

2.1 Diagnosis, staging and prognosis

Kaposi sarcoma is still the most common tumour in people with HIV infection, is an AIDS-defining illness and is caused by the Kaposi sarcoma herpesvirus (KSHV). The diagnosis is usually based on the characteristic appearance of cutaneous or mucosal lesions and should be confirmed histologically since even experienced clinicians misdiagnose KS [1] (level of evidence 1C). Lesions are graded histopathologically into patch, plaque or nodular grade disease. Visceral disease is uncommon, affecting about 14% at diagnosis [2] and CT scans, bronchoscopy and endoscopy are not warranted in the absence of symptoms (level of evidence 2D).

The AIDS Clinical Trial Group (ACTG) staging system for AIDS-related KS was developed in the pre-HAART era to predict survival and includes tumour-related criteria (T), host immunological status (I) and the presence of systemic illness (S) (see Table 2.1) [3,4]. The ACTG also established uniform criteria for response evaluation in AIDS KS (see Table 2.2) [3]. In the era of HAART the prognostic value of this staging system has been questioned and one study suggested that only the T and S stages identify patients with poor survival [5], whilst another study from Nigeria found that I and S stages but not T stage were of prognostic significance [6]. However, a comprehensive evaluation of prognostic factors in 326 patients diagnosed with AIDS KS in the era of HAART, externally validated on 446 patients from the US HIV/AIDS Cancer Match Study, has established a prognostic scoring scheme [7] and more detailed immune subset analysis does not provide additional prognostic information [8]. Having KS as the first AIDS-defining illness (-3 points) and increasing CD4 cell count (-1 for each complete 100 cells/µL in counts at KS diagnosis) improved prognosis, whereas age at KS $\geq$50 years old (+2) and S1 stage (+3) conveyed a poorer prognosis. On the basis of this index it was suggested that patients with a poor risk prognostic index (score >12) should be initially treated with HAART and systemic chemotherapy together whilst those with a good risk (score <5) should be treated initially with HAART alone, even if they have T1 disease. Over time, there has been a rise in the CD4 cell count at diagnosis of KS, and the impact of initiation of treatment may also change [9-12].

In addition to prognostic factors identified in the model, blood levels of Kaposi sarcoma herpesvirus (KSHV) DNA are a surrogate marker of tumour burden and are of prognostic significance. In 144 patients followed in the Swiss HIV Cohort study, detectable levels KSHV DNA in the blood is a poor prognostic indicator [13]. Patients in Zimbabwe initiated on ART for advanced AIDS-KS, also had a poorer outcome when pre-treatment plasma KSHV levels were high [14].

Table 2.1 The modified AIDS Clinical Trials Group staging of KS [3,4]

TIS staging of KS	Good risk (all of the following)	Poor risk (any of the following)
(T) Tumour	Confined to skin, lymph nodes or minimal oral disease	Tumour-associated oedema or ulceration Extensive oral KS Gastrointestinal KS KS in other non-nodal viscera
(I) Immune status	CD4 cell count >150cells/μL	CD4 cell count <150 cells/μL
(S) Systemic illness	Karnovsky performance status >70	Karnovsky performance status <70 or other HIV-related illness

Table 2.2 Response criteria for HIV-associated Kaposi sarcoma [3]

Complete response (CR)

The complete resolution of all KS with no new lesions, lasting for at least 4 weeks. A biopsy is required to confirm the absence of residual KS in flat lesions containing pigmentation. Endoscopies must be repeated to confirm the complete resolution of previously detected visceral disease.

Clinical complete response (CCR)

Patients who have no detectable residual KS lesions for at least 4 weeks but whose response was not confirmed by biopsy and/or repeat endoscopy.

Partial response (PR)

One or more of the following in the absence of (i) new cutaneous lesions, (ii) new visceral/oral lesions, (iii) increasing KS-associated oedema, (iv) a 25% or more increase in the product of the bidimensional diameters of any index lesion:

1. A 50% or greater decrease in the number of measurable lesions on the skin and/or in the mouth or viscera.
2. A 50% or greater decrease in the size of the lesions as defined by one of the following three criteria:

(a) a 50% or more decrease in the sums of the products of the largest bidimensional diameters of the index lesions;

(b) a complete flattening of at least 50% of the lesions;

(c) where 75% or more of the nodular lesions become indurated plaques.

Stable disease (SD)

Any response that does not meet the above criteria

Progressive disease (PD)

Any of the following:

1. A 25% or more increase in the product of the bidimensional diameters of any index lesion;
2. The appearance of new lesions;
3. Where 25% or more of previously flat lesions become raised;
4. The appearance of new or increased KS-associated oedema.

2.2 Management

2.2.1 Prevention

The introduction of HAART was associated with a substantial reduction in the incidence of KS in many large cohorts [15-21], although some of this decline in incidence appears to have preceded the introduction of HAART [22]. A population-based, record-linkage study of 472,378 individuals living with AIDS described a fall in the cumulative incidence of KS from 14.3% during 1980–1989, to 6.7% during 1990–1995, and a further fall to 1.8% during 1996–2006 [23]. Similarly, survival rates from KS have risen gradually during this period [24-26]. In contrast, KS continues to be a significant problem in Africa [27-32] though it is hoped that with increasing access to HAART, outcomes will improve [33-35]. The decline in incidence of KS has been shown to be attributable to HAART and NNRTI-based regimens are as effective as PI-based regimens in preventing KS [16,36]. Moreover, the SMART study assigned 5472 patients to continuous or intermittent use of ART, guided by CD4 cell count, and it found that the drug conservation arm had higher rates of KS (1.9 per 1000 person-years versus 0.3, hazard ratio 7.0) [37], as well as opportunistic infections and deaths. The optimal time to start HAART for asymptomatic HIV infection is still unclear, and is being addressed in the Strategic Timing of AntiRetroviral Treatment (START) study, an ongoing multicentre international trial designed to assess the risks and benefits including prevention of KS, of initiating HAART earlier than currently recommended [38].

Specific therapies against KSHV, the cause of KS, may also be helpful in the prevention of KS but published retrospective cohort studies are contradictory. A UK cohort study of 3688 people living with HIV showed that the risk of KS was reduced by ganciclovir and foscarnet exposure but not aciclovir [39]. However, data from a cohort of 935 MSM living with AIDS found that neither aciclovir, ganciclovir nor foscarnet significantly reduced the risk of KS [40]. A small randomized controlled cross-over trial of oral vanganciclovir in 26 men reduced the frequency and quantity of KSHV replication, but this returned to baseline levels soon after stopping therapy [41]. HAART results in significant falls in the levels of oropharyngeal KSHV, whereas valaciclovir and famciclovir have only a modest effect that is not synergistic with HAART [42].

2.2.2 Local therapy

Local treatments are most useful for managing localised or symptomatic KS lesions or for cosmesis. However, local therapies are limited by their inability to treat large areas or to affect the development of lesions in untreated areas.

2.2.2.1 Radiotherapy

During the pre-HAART era radiotherapy had an important and established role in the management of low volume cutaneous KS, including the cosmetic control of skin lesions, treatment of painful lesions on soles, genitalia, oral cavity and conjunctiva [43]. An early randomized study of radiation fractionation for cutaneous KS showed that both response rate and duration of local control were better with fractionated regimens (40 Gy in 20 fractions and 20 Gy in 10 fractions) compared with an 8 Gy single fraction, although toxicity and patient convenience were worse [44]. A second non-randomized study of 57 patients

found no significant difference in response rates between 16 Gy in 4 fractions and 8 Gy in a single fraction [45]. A retrospective study of 80 patients including some with endemic KS treated with a radiotherapy dose of 8 Gy reported an objective response rate of 74% [46]. In another study of 36 patients with KS of the feet, a schedule of 3 fractions/week at 3.5 Gy/fraction up to a total dose of 21 Gy, the response rate was 91% with a complete response rate of 80% [47]. A randomized trial compared two regimens: 24 Gy in 12 fractions and 20 Gy in 5 fractions with similar biologically equivalent doses, 28.8 and 28 Gy, respectively [48]. Eighty sites in 60 patients (10 of whom were on HAART) were randomized, though 13 patients died before receiving radiotherapy. A total of 65 sites in 47 patients were treated, 50 on the lower limbs, with a median area treated of 714 cm^2. Objective response rates, acute and late toxicities were similar in both arms, with a mean time to response of 3 months. An important large randomized study from Zimbabwe has evaluated treatments for AIDS-KS in 495 patients who were not treated with antiretroviral agents. This showed that radiotherapy did not improve either overall survival or quality of life compared to supportive care alone [49]. In conclusion, higher numbers of fractions of radiotherapy appear to offer only minor benefits and are more costly as well as being less convenient for patients.

In vitro models suggest a radiosensitizing effect of HIV, though it is not clear if this is of clinical relevance [50]. Radiotherapy side effects in patients with AIDS have been reported as more severe [43,51], although a recent review of head and neck cancer patients treated with high-dose radiotherapy or chemoradiotherapy did not show any significant increase in toxicity for HIV-positive compared to HIV-negative patients [52]. Modified fractionated schedules and close attention to skin care including avoidance of friction and sparing use of moisturisers may help.

The use of radiotherapy has declined since the introduction of HAART, although it may still be useful for KS at specific sites; for example, ^{90}Strontium brachytherapy is an effective and well-tolerated treatment for eyelid and conjunctival lesions [53].

2.2.2.2 Other local therapies

Retinoids bind nuclear hormone receptors, resulting in profound effects on cellular differentiation and programmed cell death and can inhibit KS cell lines *in vitro* [54]. Alitretinoin gel (0.1%) (9-cis-retinoic acid) is a topical, self-administered therapy approved in the US and some European countries, for the treatment of KS. Two double-blind, randomized placebo-controlled trials involving a total of 402 individuals, evaluated 12 weeks of twice-daily alitretinoin gel [55,56]. The response rates in the active arm after 12 weeks were 37% [56] and 35% [55] compared to 7% and 18% in the placebo arms analysed by intention to treat. In both studies over 80% participants were receiving HAART and this did not influence the results. In another study of 114 patients, 27% treated lesions responded compared to 11% of the controls [57]. The gel may cause dermal irritation and skin lightening at the application site. Responses are seen even in patients with low CD4 cell counts and typically occur 4–8 weeks after treatment. 9-cis-retinoic acid has also been administered orally (and is only licensed in UK for chronic eczema). In a phase II study of 57 patients (56 on HAART), the response rate was 19% although the contribution of the HAART is unclear [58].

Vinblastine is the most widely used intralesional agent for KS and responses of around 70% were reported in the pre-HAART era [59,60]. Treated lesions usually fade and regress although typically do not resolve completely. A randomized study in 16 patients comparing intralesional vinblastine or sodium tetradecyl sulphate in the treatment of oral KS demonstrated partial responses in both groups with no significant differences [61]. Intralesional injections of biologic agents such as interferon-α have also shown activity, but are infrequently used now.

In one early study of 20 patients, complete responses were observed in 80% of lesions treated with cryotherapy, and the duration of the response was more than 6 weeks. Greater than 50% cosmetic improvement of KS was reported in this pre-HAART era study [62]. An alternative experimental approach is photodynamic therapy, which is based upon activation by light of a photosensitising drug that preferentially accumulates in tumour tissues such as KS [63]. A series of 25 patients with a total of 348 KS lesions received photofrin 48 hours prior to light activation. No patients were on HAART and 95% of the lesions responded to therapy (33% and 63% complete and partial responses, respectively) [64].

Topical halofuginone is an angiogenesis inhibitor that inhibits collagen type-1 and matrix metalloproteinases (MMPs). It was tested in a blinded intra-patient control study for KS, with serial biopsies taken from index lesions [65]. The study was stopped early due to slow accrual, and clinical benefit could not be assessed. To a large extent local therapies for KS have been superseded by the introduction of HAART.

2.2.3 Systemic therapy

2.2.3.1 HAART

There are no randomized trials comparing HAART with no HAART as all patients with KS should receive HAART. Many case reports and small series have described the regression of KS with HAART alone. HAART has been shown to prolong time to treatment failure after KS treatment with local or systemic therapy [66]. HAART has also been shown to prolong survival in patients who have been treated for KS with chemotherapy [67].

The beneficial effects of HAART on both the incidence and the outcomes of KS have been shown in several cohort studies [20,68-71]. The Swiss HIV Cohort Study reported step-wise falls in the relative risk of KS from the pre-HAART (1985–1996) to the early-HAART era (1997–2001), and continuing reduction in the late-HAART era (2002–2006) [72]. With the increasing roll out of HAART, these benefits have also started to be seen in Africa [33,36].

Initiation of HAART may precipitate a paradoxical worsening of symptoms, termed the immune reconstitution inflammatory syndrome (IRIS). Opportunistic infections are the most common manifestation, although sudden progression of existing KS or development of new lesions may also occur [73-76]. A systematic review identified 54 cohort studies of 13,103 patients starting HAART, of whom 1699 developed IRIS, 6.4% of whom had KS [77]. Conversely the frequency of IRIS KS in patients with KS who start HAART varies between different populations but is up to 29% in a recent publication from Chicago [76]. Risk factors for IRIS KS include a higher CD4 cell count, the presence of oedema and the use of protease inhibitors and nonnucleosides together [73]. The clinical management of IRIS KS is usually with systemic chemotherapy and this has been successful in a small series of patients [78] and several case reports [79-82].

2.2.3.2 Cytotoxic chemotherapy

Administration of systemic cytotoxic chemotherapy is warranted in patients with advanced, symptomatic or rapidly progressive KS. It has been suggested that patients with a poor prognostic risk index (score >12) should be initially treated with both HAART and systemic chemotherapy together whilst those with a good risk (score <5) should be treated initially with HAART alone, even if they have T1 disease [7]. A recent randomized study from South Africa compared the response rates and survival in AIDS-KS patients treated with HAART alone or with HAART and chemotherapy. At enrolment, 89% of the 112 HAART-naive patients had advanced T1 stage KS. Of note both the chemotherapy (adriamycin, bleomycin, vincristine) and the HAART regimen used in this trial (lamivudine, stavudine, nevirapine) are not current first-line standards of care in economically developed nations. Patients randomized to HAART with chemotherapy had significantly higher response rates and progression-free survival although no difference in overall survival [83]. The lack of a significant difference in overall survival may be because many people with AIDS-KS die of other causes associated with advanced immunosuppression including opportunistic infections. These results suggest that patients with T1 advanced stage KS, should receive chemotherapy along with HAART (level of evidence 1b).

In the pre-HAART era, several chemotherapeutic agents (bleomycin, vinblastine, vincristine and etoposide) were shown to have activity against KS in case series and small Phase II trials using different combinations and doses of these drugs [84-88]. However, liposomal anthracyclines and taxanes have become established as the backbone of current standard systemic cytotoxic therapy against KS.

2.2.3.3 Liposomal anthracyclines

Liposome encapsulation of anthracyclines constitutes a considerable advance in the chemotherapy of KS. The advantages of liposomal formulation include increased tumour uptake and hence favourable pharmacokinetics and toxicity profile. The trials of liposomal anthracyclines for HIV-associated KS were undertaken in the pre-HAART era but clinicians continue to regard them as the gold-standard first-line chemotherapy for KS. Previous manufacturing problems leading to interruptions in supply have been resolved. Both liposome encapsulated daunorubicin (DaunoXome 40mg/m^2 every 2 weeks) and the pegylated liposomal doxorubicin, which is known variously as Caelyx, Doxil or PLD (20mg/m^2 every 3 weeks) have been shown to have good antitumour activity. A meta-analysis of 2200 patients treated in nine randomized controlled trials, including two for KS patients demonstrated that the toxicity profile compares favourably with that of conventional anthracyclines [89]. A report of 93 patients treated at a single centre has found no evidence of cardiotoxicity even at high cumulative dosages [90] and rarely significant alopecia. However, there remains considerable myelosuppression, and occasional emesis. In addition, infusion-related hypotension and hand/foot syndrome are novel side effects seen with these liposomal formulations.

Three sizeable, randomized controlled studies have compared liposomal anthracyclines with conventional combination chemotherapy regimens and all were conducted before the introduction of HAART. A phase III randomized comparison of DaunoXome and ABV (doxorubicin, bleomycin, vincristine) demonstrated equivalent overall response rates (partial and complete responses), time to treatment failure and survival duration [91]. Two

randomized phase III trials compared pegylated liposomal doxorubicin (PLD) with conventional combination chemotherapy: ABV in one study and BV (bleomycin vincristine) in the other, as first-line therapy for KS in patients not on HAART. Both found response rates were higher in the PLD arms but responses were often not sustained [92,93] (see Table .3 for details). The three phase III studies may not be directly comparable. In one small randomized study of 80 patients, KS patients were randomized 3:1 to PLD (20mg/m^2) or Daunoxome (40 mg/m^2) every 2 weeks for up to six cycles. Partial responses, correlating with clinical benefit, were observed in 55% patients receiving PLD and in 32% receiving Daunoxome. However, this was not statistically significant and there is insufficient evidence to recommend a particular liposomal anthracycline [94].

Since the widespread introduction of HAART, the duration of responses to treatment for KS has increased [66] and no further randomized trials have compared liposomal anthracyclines with non-encapsulated anthracycline-based regimens. The safety and tolerability of these drugs in combination with HAART has been evaluated. In one study of 54 patients, 82% had a response within 8 weeks and the PLD-HAART combination was well tolerated with no evidence of suppression of CD4 cell counts [95]. In a cohort study of 50 patients treated with concomitant HAART and liposomal anthracycline chemotherapy for KS, there was no decline in CD4 cell count or rise in HIV viral load [96]. These findings suggest that standard opportunistic infection prophylaxis guidelines may be followed when treating patients with liposomal anthracycline chemotherapy for KS. Based on the response rates, median response durations and the toxicity profile, liposomal anthracyclines are considered first-line chemotherapy for advanced KS (level of evidence 1A).

Table 2.3 Results of phase III trials of liposomal anthracyclines for KS

Agent	Dose	Schedule	Assessable patients	Response rate (CR + PR)	Median response duration (months)	*P*	Ref
Daunoxome	40mg/m^2	Every 2 weeks	116	25%	3.8	NS	[91]
ABV	10mg/m^2/15U/1mg/	Every 2 weeks	111	28%	3.2		
Doxil/Caelyx/PLD	20mg/m^2	Every 2 weeks	133	46%	3.0	<0.001	[92]
ABV	20mg/m^2/10U/m^2/1mg/	Every 2 weeks	125	25%	-		
Doxil/Caelyx/PLD	20mg/m^2	Every 3 weeks	121	59%	5.0	<0.001	[93]
BV	15U/m^2/2mg	Every 3 weeks	120	23%	-		
Doxil/Caelyx/PLD	20 mg/m^2	Every 2 weeks	60	55%	5.0	NS	[94]
Daunoxome	40 mg/m^2	Every 2 weeks	19	32%	-		
Doxil	20 mg/m^2	Every 3 weeks	37	46%	12.2*	NS	[94]
Paclitaxel	100 mg/m^2	Every 2 weeks	36	56%	17.5*		

* 53 out of the 73 patients (73%) were on HAART at baseline

2.2.3.4 Taxanes

Like vinca alkaloids, taxanes bind to the β subunit of α/β tubulin and disrupt microtubules leading to mitotic arrest and subsequent cell death. Paclitaxel also promotes apoptosis by binding to Bcl-2 via the same mechanism [97]. In a number of phase II trials, paclitaxel was shown to have single agent activity against AIDS-KS; furthermore these studies included a number of patients who had previously received anthracyclines [98-102]. One phase II study of paclitaxel (135mg/m^2 every 3 weeks) for KS enrolled 28 patients and reported a response rate of 71%. This included four (14%) patients who had received anthracyclines but no patients received HAART [99]. A second, larger study of 56 patients included 20 (36%) who received a protease inhibitor at some stage during the study and 40 (70%) who had received prior therapy for KS that included liposomal anthracyclines in 17 (30%). The overall objective response rate was 59% and the median response duration was 10.4 months [100].

A first-line study for advanced, symptomatic KS randomized 73 patients between paclitaxel 100 mg/m^2 every weeks and PLD 20 mg/m2 every 3 weeks; 73% patients received HAART (see Table 3) [103]. Treatment was associated with significant improvements in pain and

swelling, for both arms. There was no significant difference between the arms in response rates, progression-free or overall survival at 2 years, and slightly higher rates of grade 3-4 toxicity for paclitaxel (84% vs 66%, p=0.07). Progression-free survival for both arms in this study was higher than those reported in the pre-HAART era. Pharmacokinetic studies revealed higher paclitaxel levels in patients taking protease inhibitors, though this did not have any obvious clinical impact [104].

Two studies have addressed the role of paclitaxel as second-line chemotherapy. One open-label multicentre trial enrolled 107 individuals who had received prior chemotherapy for AIDS-KS. The previous therapy regimens included ABV (adriamycin, bleomycin, vincristine) in 52, liposomal daunorubicin in 49, and liposomal doxorubicin in 40 patients. Moreover, only 77% were receiving concomitant HAART (all protease inhibitor based) and 33% started this treatment at the same time as the taxane chemotherapy. The paclitaxel protocol used was 100mg/m^2 fortnightly. The overall response rate was 56% with no significant difference in response rate when comparing patients on or not on HAART. Less surprising was the finding that patients on HAART had a significantly improved survival. The main side effect reported in these studies was neutropenia that generally resolved prior to the next chemotherapy cycle [101].

In a second study of 17 patients with anthracycline refractory AIDS-KS, defined as KS that had progressed during or within 6 months of completing liposomal anthracycline chemotherapy. All patients were receiving a stable HAART regimen to avoid confounding of results. The treatment schedule was again 100mg/m^2 fortnightly. The objective response rate to paclitaxel was 71% (95% CI: 60–81), 8/17 partial responses and 4/17 complete responses. There were no significant changes in CD4, CD8, CD16/56 (natural killer cells) and CD19 (B cells) lymphocyte subset cell counts during and for up to one year following chemotherapy. Similarly, plasma HIV-1 viral loads did not change significantly during or after treatment suggesting that the combined use of paclitaxel and HAART reduces the risk of chemotherapy related immunological decline and opportunistic infections [102]. In contrast, previous trials without concomitant HAART were worrying in this respect; Gill reported 51 AIDS-defining opportunistic infections in the 56 patients treated with paclitaxel (10.5/100 patient months on paclitaxel), only 36% of whom received HAART, and Welles reported 27 opportunistic infections (8.4/100 person months on paclitaxel) among her cohort of 28, none of whom received HAART [99]. Thus the concomitant use of HAART and paclitaxel appears to be safe and not detrimental to immune function despite initial concerns over pharmacological interactions [104-106]. These findings suggest that standard opportunistic infection prophylaxis guidelines may be followed when treating patients with taxane chemotherapy for KS.

The higher rates of toxicity and the need for a 3-hour infusion make paclitaxel a less attractive first-line option than PLD [103]. The clinical experience in KS with docetaxel, another taxane, is much more limited though two small studies suggest that this agent can produce meaningful responses when used weekly [107], and in anthracycline pre-treated individuals [108]. However, severe toxicities, including one death, have been reported in patients prescribed docetaxel with ritonavir-boosted protease inhibitors. [109,110]. The mechanism for this enhanced toxicity is a pharmacokinetic interaction as docetaxel is metabolised by CYP3A4, which is inhibited by ritonavir. This pathway is less important in the metabolism of paclitaxel.

2.2.3.5 Immunotherapy

The biological response modifier interferon-α (IFN-α) was approved for KS treatment before the availability of HAART and liposomal anthracyclines. The ACTG randomized 68 individuals to low- and intermediate dose IFN-α (1 million and 10 million units daily) plus didanosine [111]. Response rates and durations were not statistically different though there were more toxicities in the higher dose group. In another randomized study, 108 patients were treated with IFN-α (1 million or 8 million units daily) with AZT [112]. The higher-dose regimen was associated with statistically higher responses and longer time to progression. In a retrospective study of patients with classic KS comparing PLD with low dose IFN-α, 12 patients received 20 mg/m^3 of PLD monthly while six received 3 million units of IFN-α three times per week with PLD being superior in terms of responses and toxicity [113].

Response to IFN-α frequently requires continued treatment for 6 months or more, as the time to response is typically more than 4 months. It should not be considered for progressive or visceral disease. Toxicity at higher doses including fever, chills, neutropenia and depression is common, and poor responses are observed in the setting of low CD4 cell counts. While it can be considered in those with residual KS who have appropriately reconstituted their immune systems with HAART, it is seldom used.

2.2.3.6 Other systemic therapies

With greater understanding of the biology of KS and the cellular pathways activated in these tumours, novel targets for treatment have been identified. In many clinical trials the effects of the experimental drug and of HAART are difficult to separate, often because of poor trial design.

Vascular endothelial growth factor-A (VEGF-A) is an important growth factor in KS and seems to be responsible for vascular permeability [114,115]. Bevacizumab, a humanized, monoclonal, anti–VEGF-A antibody has been used in a phase I/II study in 17 patients with advanced disease, 13 of whom had had prior chemotherapy [116]. The overall response rate was 31% and median progression free survival 8.3 months. Apart from a fall in IL-8, there were no other immune markers of response, and serum VEGF-A levels did not change.

Thalidomide also has significant anti-angiogenic activity and two phase II studies enrolled a total of 37 AIDS-KS patients. Partial responses were recorded for 35% and 47% evaluable patients with toxicity including fatigue, neuropathy and depression [117,118]. The importance of the c-kit pathway has been evaluated in 30 patients with previously treated cutaneous KS who received oral imatinib; 10 (33.3%) achieved a partial response while six (20%) had stable disease. Treatment was relatively well tolerated, with nine patients completing 52 weeks of therapy [119]. Other agents tested include COL-3, a matrix metalloproteinase inhibitor (MMPI), which in a phase II trial of 75 patients, demonstrated partial responses in 41% [120]. However, in a phase I/II trial, BMS-275291, a more specific oral nonpeptidic MMPI, was poorly tolerated and did not show any meaningful responses [121]. Similarly, interleukin 12 was administered to patients on HAART with KS and the response rate was 71% [122]. Valproic acid has properties of an HDAC inhibitor with some activity *in vitro*, but a pilot study in 18 patients did not show any promising efficacy [123]. PI3K/AKT/mTOR signalling is a common pathway downstream of many growth factor and cytokine receptors and is upregulated by KSHV encoded proteins. Rapamycin, an oral

immunosuppressant used to prevent rejection in solid organ transplantation, has activity in AIDS-KS but has significant pharmacokinetic interactions with HAART [124].

Topoisomerase I and II enzymes play a critical role in KSHV DNA replication, and type I inhibitors such as irinotecan and topotecan, and type II poisons, such as etoposide [125,126] and doxorubicin have significant cytotoxic activity but with dose-limiting toxicities including myelosuppression. Topoisomerase II catalytic inhibitors such as novobiocin, in contrast, show marked inhibition of KSHV replication and minimal cytotoxicity and may be a promising therapeutic alternative [127].

A number of anti-herpes virus agents have been studied in AIDS-related KS; none has demonstrated significant activity, although they have been shown to prevent KS in one cohort study [39]. KSHV stimulates expression of angiopoietin-2 in KS via upregulation of the Ras/Raf/MEK/ERK pathway. Selumetinib is an oral selective inhibitor of MEK1/2 with anticancer activity in a variety of tumour models[128] and is being tested in a Phase I/II study for AIDS-KS patients.

Where possible, patients should be considered for appropriate clinical trials.

2.3 Summary of recommendations

We recommend that KS should be confirmed histologically (level of evidence 1C).

We suggest that CT scans, bronchoscopy and endoscopy are not warranted in the absence of symptoms (level of evidence 2D).

We recommend that HAART should be started in all patients diagnosed with KS (level of evidence 1B)

We suggest local radiotherapy or intralesional vinblastine for symptomatic or cosmetic improvement in early stage T0 KS (level of evidence 2C)

We recommend that patients with T1 advanced stage KS, should receive chemotherapy along with HAART (level of evidence 1B).

We recommend that liposomal anthracyclines (either Daunoxome 40mg/m^2 q14d or Caelyx 20mg/m^2 q21d) are first-line chemotherapy for advanced KS (level of evidence 1A).

We recommend paclitaxel chemotherapy for second-line treatment of anthracycline refractory KS (level of evidence 1C).

All patients should be considered for clinical trial enrolment if eligible (GPP).

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3.0 Systemic AIDS-related non-Hodgkin lymphoma (ARL)

3.1 Introduction

People living with HIV have an increased risk of developing non-Hodgkin lymphoma (NHL) [1-4]. The two commonest subtypes are diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma/leukaemia (BL), which are considered AIDS-defining illnesses (ADI). NHL is the second most common tumour in individuals with HIV and although studies show a decline in incidence since the introduction of HAART [5-8], AIDS-related lymphomas (ARLs) have increased as a percentage of first ADI [9,10]. The development of ARL has been shown to be related to older age, low CD4 cell count and no prior treatment with HAART [11]. Patients tend to present with advanced clinical stage, B symptoms and extra-nodal involvement, including bone marrow.

Before the introduction of HAART, the outlook for patients with ARL was poor, with the median survival for patients treated with chemotherapy being around 2–13 months. Median survival in the post-HAART era is beginning to approach that observed in the HIV-negative population and depends critically on histological subtype and stage of disease [12-20].

3.2 Diagnosis, staging and prognosis

The diagnosis of ARL should be based on a tissue biopsy rather than a cytological sample. In addition to the routine investigations advised as part of HIV clinical care, all patients require staging with clinical evaluation, blood tests, computerised tomography (CT) scanning and bone marrow aspiration and trephine (Table 3.1). -fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F-FDG PET) scanning at diagnosis improves the staging accuracy and the Imaging Subcommittee of the International Harmonisation Project in Lymphoma has produced guidelines strongly recommending a baseline pre-treatment ^{18}F-FDG PET scan [21]. Cerebrospinal fluid (CSF) examination is recommended if there are clinical signs of central nervous system (CNS) disease, or paranasal sinus, breast, epidural or testicular involvement. Cytological assessment by cytospin and flow cytometry is recommended [22]. Indications for intrathecal prophylaxis will be outlined in BCSH guidelines and should be administered at time of first CSF examination in these patients. Patients with BL are at a particularly high-risk of developing CNS disease [23] and thus treatment should incorporate CNS-penetrating chemotherapy in all patients with BL. Staging should be according to the Ann Arbor classification/Cotswolds modification system [24].

Prognostic factors for survival in the pre-HAART era were predominantly immunological (prior ADI and low CD4 cell count) [25,26]. Factors that are associated with survival in the post-HAART era are the International Prognostic Index (IPI) score (Table 2) [17,27] and in some studies, the CD4 cell count at diagnosis, with a CD4 cell count less than 100 cells/µL predictive of a worse outcome [28]. In two studies performed by the AIDS-Malignancies Consortium (AMC) in the US, patients with a CD4 count of <50 cells/µL treated with either R-CHOP or R-EPOCH experienced a high rate of infection-related mortality (35–40%) [19,27]. Whether improved infection surveillance and prophylaxis or alternative approaches are

warranted for this subgroup remains unclear, as this has not been noted in other studies [29].

It is recommended that all patients have pathology and treatment plans reviewed by a specialist multidisciplinary team (MDT) and that management is co-ordinated closely with an HIV physician and a haemato-oncologist familiar with the treatment of such patients.

Table 3.1. BHIVA recommendations for baseline investigations* in DLBCL and BL

Haematology: FBC, blood film, ESR, blood group and screen, consider coagulation screen
Serum chemistry: renal and liver function, bone profile, LDH, urate, CRP, immunoglobulins, serum protein electrophoresis, β-2 microglobulin
Virology: HbsAg, HbsAb, HbcAb, anti HCV, VZV IgG, CMV IgG
Lumbar puncture: this is not a routine staging investigation. If performed because IT prophylaxis is indicated according to BCSH/local guidelines: CSF protein. CSF glucose, CSF cytology with flow cytometry should be performed
ECG
CXR
Bone marrow (BM) biopsy and aspirate
Neck-chest-abdomen-pelvis (NCAP) CT scan with contrast unless contra-indicated
^{18}F-FDG PET-CT scan
Other investigations if clinically indicated (MRI, ECHO, MUGA)

*Tests in addition to routine HIV clinical care investigations

Table 3.2 International prognostic index for aggressive non-Hodgkin's lymphoma [30]

Score 1 for each factor present:
Age >60 years
Serum LDH >normal
Performance status >1
Stage III/IV
Extranodal site >1
Final IPI risk group
0 or 1, low risk;
2, low intermediate risk;
3, high intermediate risk;
4 or 5, high risk

Table 3.3 Outcome of DLBCL according to the IPI score in HIV-negative patients treated with rituximab, adapted from Sehn *et al*. [31].

Risk group	Number of adverse factors	% of patients	4-year PFS*	4-year OS*
Low risk	0–1	28%	85%	82%
Intermediate-low	2	27%	80%	81%
Intermediate-high	3	21%	57%	49%
High-risk	4–5	24%	51%	59%

Risk factors: age >60; LDH >ULN; stage III–IV; PS ECOG ≥2; extra-nodal sites ≥2

**data on HIV-negative patients treated with R-CHOP*

Revised-IPI[#]

Risk group	Number of adverse factors	% of patients	4-year PFS	4-year OS
Very good	0	10%	94%	94%
Good	1–2	45%	80%	79%
Poor	3–5	45%	53%	55%

Risk factors: age >60; LDH >ULN; stage III-IV; PS ECOG ≥2; extra-nodal sites ≥2

[#] *'Revised-IPI' includes the same prognostic factors as the IPI but differs in the distribution of risk-group according to the number of adverse prognostic factors*

Table 3.4. Outcome of DLBCL according to IPI score in HIV-positive patients (adapted from [32])

IPI risk group (no. of patients)	Complete responses to chemotherapy (%)	3-yr survival (%)
Low (42)	63	64
Low intermediate (35)	64	64
High intermediate (13)	28	50
High (11)	13	13

3.3 Management

3.3.1 First-line chemotherapy for DLBCL in HIV-infected individuals

Prior to the introduction of HAART, treatment with standard dose chemotherapy induced high levels of toxicity. Improvements in chemotherapy response rates were generally offset by increased death due to opportunistic infection [33,34]. The introduction of HAART has

led to better control of HIV viral replication and improved immune function, and the incorporation of haematopoietic growth factors (G-CSF) into treatment protocols has allowed for the introduction of increasingly myelotoxic regimens. This has allowed conventional chemotherapy regimens in use in the HIV-negative setting, such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), to be used as first-line treatment in HIV-positive patients and outcomes are now similar for those with and without HIV infection [15,16].

The infusional regimen, dose-adjusted (DA) EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and hydroxydaunorubicin) has been favoured over CHOP chemotherapy, in some US centres, due to superior response rates, survival and lower rates of infectious death observed when compared to historical data [18-20,35]. The DA-EPOCH regimen is based on *in vitro* studies demonstrating that prolonged exposure to low doses of chemotherapy agents can overcome tumour resistance as compared to brief exposure to high concentrations [36,37]. Dose adjustment to the neutrophil nadir minimises haematological toxicity [38]. However, CHOP and EPOCH have not been compared in a randomized study. The outcome after the infusional chemotherapy regimen of cyclophosphamide, doxorubicin and etoposide (CDE), administered as a 96-hour continuous infusion, has also been reported in single and multi-centre series [39-41], and although patients who received HAART did better, the outcome has not been compared directly to CHOP. These reports are consistent with those for DLBCL in HIV-negative patients where CHOP is considered the standard therapy for most patients treated in the UK, as no survival advantage has been demonstrated for any other chemotherapy regimen in a randomized study [42-44].

3.3.1.1 Localised disease

Localised DLBCL usually refers to patients with stage I disease. However, some patients with stage II disease, where the disease can be incorporated into a single radiotherapy field, are sometimes referred to as having localised disease. A minority of HIV-infected patients (10–30%) present with localised disease [14,17,27], and for these patients either combined-modality treatment with 3 cycles of chemotherapy followed by radiotherapy or chemotherapy alone (4–8 cycles) are valid options. In the HIV-negative setting there continues to be debate as to which approach is best, with some studies demonstrating the superiority of chemotherapy alone [45], whilst others showing a benefit for combined-modality treatment [46]. Although radiotherapy may decrease the risk of recurrence at the site of initial disease, it does not prevent distant recurrence [47]. These studies all differ in design, patient characteristics, the type of chemotherapy and the number of cycles administered, Thus, the decision as to which approach to use will depend on the toxicity associated with irradiating a particular disease site and patient/physician choice.

3.3.1.2 Disseminated disease

In the UK, the most commonly used chemotherapy combination in both the HIV-positive and negative setting is CHOP-21. In disseminated disease, a minimum of 6 cycles are given or 2 cycles beyond documentation of a complete response (CR) (i.e. a maximum of 8 cycles). This is extrapolated from data generated in HIV-negative patients, in which studies have used either 6 or 8 cycles of chemotherapy, but with no direct comparison [48,49].

3.3.2 Rituximab for DLBCL

The role of rituximab (R) in HIV-associated B-cell lymphomas has been controversial ever since a randomized phase III study conducted by AMC in the US of CHOP versus R-CHOP, in patients with aggressive B-cell lymphoma was published [27]. This trial compared R-CHOP (*n*=99) with CHOP (*n*=50), using a standard rituximab dose of 375 mg/m^2 with each cycle of chemotherapy but also included maintenance rituximab every 3 months in those who responded to R-CHOP [39]. Although there was a trend to improved response rate with rituximab, (58% vs 47%, *P*=0.15), a significant reduction in progression of lymphoma on treatment, and in death due to lymphoma, an increased death rate from infectious complications, particularly (9/15) in those with a CD4 cell count below 50 cells/μL, was observed. Six of 15 deaths occurred during the maintenance phase of rituximab, a strategy not used in aggressive NHL in HIV-negative patients and this sub-group analysis was post-hoc, not pre-planned. However, this remains the only phase III study addressing the role of rituximab in HIV-positive patients with DLBCL. An increased risk of life-threatening infection was also observed when the results of three phase II studies were pooled, combining rituximab with the infusional CDE chemotherapy regimen in 74 patients with ARL [50]. However subsequent phase II studies of R-CHOP (without maintenance rituximab) from Europe did not show an increased risk of infectious deaths, instead showing that rituximab was beneficial [14,17].

The AMC went on to perform a randomized study of DA-EPOCH with either concurrent or sequential rituximab [19]. Concurrent administration was superior, with no increase in infectious deaths but outcome in both groups was excellent, supporting the efficacy and tolerability of concurrent rituximab. A recent meta-analysis of prospective studies has confirmed the benefit in response rate and overall survival (OS) of the addition of rituximab to chemotherapy [20]. A pooled analysis of both AMC studies mentioned above suggested that R-EPOCH resulted in superior response rates and survival compared to R-CHOP [18], although these regimens have not been compared in any randomized study. Importantly, the R-EPOCH study was performed during a later time period (2002–2006) than the R-CHOP study (1998–2002), suggesting other variables, including supportive care and antiretroviral drug options, may have differed. Consistent with this, the patients treated with R-EPOCH routinely received concurrent anti-fungal and anti-bacterial prophylaxis, which was omitted from those treated earlier with R-CHOP.

The AMC have recently reported the results of a prospective, multi-centre phase II trial of R-CHOP, but with pegylated, liposomal doxorubicin in order to limit toxicity. Of note, HAART was continued during chemotherapy. The treatment was well tolerated without any deaths from infection, even in those with a low CD4 count, thus supporting the inclusion of rituximab in treatment regimens. However, the response rate was inferior to that reported in prior studies (overall response 76.5%, CR 47.5%) [51].

Thus, the addition of rituximab to chemotherapy is now recommended for DLBCL in HIV-positive patients. Although the use of rituximab is contentious in patients with a CD4 count <50 cells/μL [27], with appropriate anti-microbial prophylaxis (co-trimoxazole, fluconazole, aciclovir, azithromycin), pre-emptive G-CSF and prompt treatment of opportunistic infection, rituximab is recommended for all patients with DLBCL. The rate of overall response (CR and partial remission; PR) and CR to R-CHOP chemotherapy is reported to be around 66–87% and 58–77% respectively [14,17,27,29]. In one study with long follow-up,

the 8 year OS was 46% [52]. (See Table 3.5 for summary of R+chemotherapy studies in HIV-positive patients).

Table 3.5. Summary of R+chemotherapy studies in HIV-positive patients

Regimen	Phase	Pts	ORR (%)(CR+PR)	CR/CRu (%)	Duration	OS	Ref
R-CHOP	III	99	65.7	57.6	PFS 45 weeks	139 weeks	[27]
R-EPOCH (Concurrent rituximab only)	II	51	88	73	2-yr PFS 66%	2-yr 70%	[53]
R-CHOP	II	81		69	8-yr 59%	8-yr 46%	[52,54]
R-CHOP	II	52	87	77	2-yr PFS 69%	2-yr 75%	[55]
R-CDE	II (3 studies pooled)	74	75	70	2-yr EFS 52%	2-yr 64%	[50]
R-EPOCH	II	33	94	91	5-yr PFS 84%	5-yr 68%	[35]

3.3.3 Treatment for high-risk patients

As mentioned, the IPI score at diagnosis is prognostic of outcome, such that those patients with high-risk disease (IPI score 3–5) have a lower response rate and overall survival to standard chemotherapy [17,27]. In the HIV-negative setting, studies have investigated intensification of chemotherapy in this high-risk group, including high-dose therapy with autologous stem cell rescue. To date, results have been heterogeneous and no clear survival benefit demonstrated [56]. This question has not been addressed in prospective studies in HIV-postive patients. However, a recent multi-centre, retrospective analysis reviewed the outcome of patients with an IPI score 3–5 and made a comparison between those treated with R-CHOP (*n*=35) chemotherapy and the more intensive regimen, CODOX-M/IVAC+/-R (*n*=15). Overall, the outcome was favourable with 68% achieving a CR and a 2-year progression-free and overall survival of 68% and 70%, respectively. There was no significant difference in remission duration, progression free survival (PFS) or OS between the two treatment groups, however, there were significantly more infections and non-haematological toxicities in the CODOX-M/IVAC+/-R group [29]. The current National Cancer Research Institute study in the UK, a phase II trial examining R-CODOX-M/IVAC in patients with DLBCL, IPI 35 has recently opened to HIV-positive patients, so will further add to clarify this question.

3.3.4 The effect of adding HAART

A comparison of 363 patients treated pre- and post- the introduction of HAART has shown that overall survival has improved in the HAART era [57]. Although tumour regressions with

immune reconstitution are rarely observed with lymphomas, optimising the immune status of the patient has been shown to reduce opportunistic infections and is associated with superior response rates and survival. Results from phase II studies and case-control series have reported higher response rates and improved survival with the addition of HAART to CHOP chemotherapy [58-62].

Opinions differ as to whether HAART should be continued during chemotherapy or not. Treatment centres in the US that use the DA-EPOCH regimen, have previously suspended HAART because of concern regarding potential adverse pharmacokinetic and pharmacodynamic interactions with chemotherapy and the potential for increased toxicity [63]. In these studies, despite a high response rate, CD4 cell counts fell dramatically during chemotherapy and took months to recover to baseline levels despite the re-introduction of HAART on completion of chemotherapy. Although this strategy did not appear to adversely affect lymphoma outcomes or increase infectious complications, the treatment groups have not been large [19,35]. There is concern that the interruption of HAART in patients on therapy prior to lymphoma diagnosis might lead to the development of viral resistance. In Europe, it is usual to continue HAART during chemotherapy, avoiding boosted protease inhibitors wherever possible as they are associated with greater toxicity and drug interactions [64]. A combined approach to care involving HIV physicians and haemato-oncologists ensures awareness that many antiretrovirals have overlapping toxicities with chemotherapeutic agents. The aim in selecting a HAART regime is to derive the potential benefits of HIV virological suppression and the associated immune reconstitution whilst minimising any potential toxicity. Again, this issue has not been examined in randomized studies.

3.3.5 Recommendations for DLBCL

Patients should be entered into clinical trials, if available (GPP).

First-line treatment of DLBCL in HIV-infected individuals includes chemotherapy regimens used in HIV-negative patients, such as CHOP or infusional therapies such as EPOCH. No randomized studies have been published in the era of ART and hence there is no optimal 'gold-standard therapy' (level of evidence 1B).

Chemotherapy regimens should be combined with HAART therapy (level of evidence 1B).

The concomitant administration of rituximab is now standard practice (level of evidence IB). Patients with CD4<50x10^6/l may require closer surveillance (GPP).

3.4 Burkitt lymphoma/leukaemia

Until recently, patients with HIV-associated BL have been treated similarly to HIV-positive patients with DLBCL. However, in a large retrospective study the survival of patients with BL was very poor when treated with CHOP or M-BACOD (methotrexate with leucovorin, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone), despite adjunctive HAART [57]. This was corroborated by the results of a phase II prospective study involving 74 patients with HIV-NHL and HIV-BL treated with rituximab and the CDE infusional regimen (R-CDE). In multivariate analysis, a diagnosis of HIV-BL was significantly associated with a worse outcome in comparison to HIV-NHL patients [50].

In the HIV-negative setting, BL is a highly curable malignancy if intensive chemotherapy regimens of short duration are combined with CNS penetrating therapy [65-67]. In the UK, the most widely used regimen is CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, methotrexate/ifosfamide, etoposide, cytarabine) and the two MRC/NCRI studies (LY6 and LY10) have stratified patients into low-risk and high-risk (Table 3.6). In low-risk disease, patients receive 3 cycles of CODOX-M and those with high-risk disease receive 4 cycles of chemotherapy alternating between CODOX-M and IVAC. Grade 3/4 haematological toxicity is universal with this regimen with a high incidence of neutropenic fever and mucositis. The reported treatment-related death rate is around 8–14% [65,66]. In the LY6 study, the main toxicity was from the use of high-dose methotrexate at a dose of 6.7g/m^2 [66] and thus in the LY10 study, the dose was reduced to 3g/m^2 [65] without compromising outcomes. In the LY10 study, the 2-year PFS and OS for low-risk disease was 85% and 88%, respectively and for high risk, 49% and 52%, respectively [65].

Table 3.6 Risk stratification for treatment of BL (adapted from the IPI score)

Low risk disease Must have at least 3 of these factors	Normal LDH Stage I or II disease WHO performance score 0–1 Number of extranodal sites ≤1
High-risk 2 or more of these factors	Raised LDH Stage III or IV disease WHO performance score 2–4 Number of extranodal sites >1

Two small retrospective and one prospective comparative studies [68-70] have demonstrated the feasibility of administering more intensive chemotherapy regimens, such as CODOX-M/IVAC [68] and hyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine) to HIV-positive patients with BL [69]. These studies report a CR rate of 63–71% and a 2-year event-free survival of 60%, similar to that observed in HIV-negative patients treated with the same regimen, with no increase in toxicity [69,70]. A retrospective study investigated concerns regarding prolonged immunosuppression and loss of viral control following intensive chemotherapy. However, in 30 HIV-positive patients with BL treated with CODOX-M/IVAC, excellent immune recovery was demonstrated with viral loads undetectable in 88% and 87% of patients at 6 and 12 months respectively following chemotherapy. In addition, the CD4 cell count was greater than 200 cells/μL in 58% and 80% of patients at 6 and 12 months, respectively [71]. These studies, although small, suggest that a uniform approach to treatment of BL should be used, regardless of HIV status

In the HIV-negative setting, it is presumed that the addition of rituximab to intensive chemotherapy will improve outcomes and its use is becoming more widespread. However,

there have not been, and are unlikely to be, randomized studies addressing this question. The feasibility of adding rituximab to CODOX-M/IVAC chemotherapy has been demonstrated in a retrospective study of 23 patients. There was no increase in toxicity and outcomes were favourable [72]. A phase II NCRI prospective study of R-CODOX-M/IVAC in BL is currently open.

The addition of R to the treatment of BL in HIV-positive patients also seems feasible. A prospective study of 36 patients with BL treated with intensive chemotherapy and rituximab, included 19 with HIV infection. Although HIV-positive patients experienced more severe mucositis and a higher incidence of infection, their outcome was not significantly different to HIV-negative patients with a CR rate of 84% and a 2-year OS of 73% [73]. A prospective phase II study from the AMC, reported in abstract form, treated patients with HIV-associated BL with a modified version of R-CODOX-M/IVAC to limit the toxicity. The 1 year OS was 82% at a median follow-up of 9 months and there were no treatment-related deaths [74]. A retrospective analysis of 80 patients with BL lymphoma treated with CODOX-M/IVAC with or without rituximab included 14 patients who were HIV-positive, 10 of whom received rituximab. The results demonstrated that there were fewer relapses in patients treated with rituximab but only a non-significant trend to improved survival. Importantly, the outcome for those with HIV infection was comparable to the HIV-negative patients [75]. A recently reported prospective study of rituximab combined with intensive chemotherapy in 118 patients with BL, included 38 HIV-positive patients [76]. HIV status did not impact on outcome and 87% of HIV-positive patients achieved a CR. With a median follow-up of 2.5 years, the 4-year probabilities for disease-free and OS were 63% and 78%, respectively. Overall, 8% of patients died during chemotherapy and those with HIV-infection had a higher incidence of grade 3/4 mucositis and severe infections.

In order to overcome concerns of treatment toxicity in HIV-associated BL, the DA-EPOCH regimen plus rituximab is favoured in the US. With a follow-up of 28 months, a study presented only in abstract form reported an impressive CR rate and OS of 100% in 24 patients treated with this regimen [77]. The studies performed in patients with BL are summarised in Table 3.7.

Table 3.7 Summary of studies performed in HIV-related BL

Regimen	Phase	Pts	ORR (%)(CR+PR)	CR/CRu (%)	Duration	OS	Reference
CODOX-M/IVAC	Retrospective	8	63	63	2-yr EFS 60%		[68]
Hyper- CVAD	Retrospective	13	100	92		2-yr 52%	[69]
PETHEMA-LAL3/97 study	Phase II	14	71	71	2-yr DFS 60%	2-yr 43%	[78]
CODOX-M/IVAC	Retrospective	30	70	57	3-yr EFS	3-yr	[71]

					75%	52%	
Rituximab plus German ALL type chemotherapy (B-ALL/B-NHL2002)	Phase II	19		84	2-yr 87%	2-yr 73%	[79]
Rituximab plus CODOX-M/IVAC	Retrospective	14*	93	93	3-yr PFS 68%	3-yr 68%	[80]
Rituximab plus German ALL type chemotherapy (B-ALL/B-NHL2002)	Phase II	38		82	4-yr DFS 77%	4-yr 63%	[76]
Rituximab plus DA-EPOCH	Phase II	8	100	100		28 month 100%	[77]

* 4 patients did not receive rituximab

3.4.1 Recommendations for BL

First-line treatment of BL in HIV-infected individuals includes regimens such as CODOX-M/IVAC and DA-EPOCH. No comparative studies have been performed and hence there is no optimal 'gold-standard- therapy' (level of evidence 1B).

Chemotherapy regimens should be combined with HAART therapy (level of evidence 1B).

The addition of rituximab is recommended (level of evidence 1C).

3.5 Prevention of secondary CNS lymphoma

The incidence of CNS involvement has been suggested to be higher in ARL compared to the HIV-negative patients with NHL [23,81] and this may reflect the more advanced stage at presentation or adverse features. Although there is no reported increase in incidence of secondary CNS lymphoma in the HIV setting there have been no specific studies that have addressed this in a randomized setting. However the outcome of secondary CNS involvement by lymphoma is very poor [82] therefore the administration of preventative treatment during first line therapy to reduce the incidence CNS relapse is a commonly adopted strategy for those patients with NHL perceived at risk. There is much debate regarding identification of these patients and the optimal strategy to adopt. Many studies [27,33,41,58-60,63,83-88] have reported the use of CNS prophylaxis and treatment in individuals with ARL, although there is a paucity of prospective or randomized trials and these studies have allowed individual institutions to administer CSF prophylaxis according to local protocol or preference. Presently a manuscript addressing these issues is in preparation by the British Committee for Standards in Haematology (BCSH) and thus this will not be discussed in detail.

Immuno-chemotherapy has significantly improved outcome in the HIV negative setting, and a number of reports suggest that the overall risk of CNS relapse has decreased with the addition of rituximab to CHOP chemotherapy [89-91] although this has not been detected in

all reports [92]. This observation supports the hypothesis that CNS relapse is less likely to occur if there is improved control of systemic disease.

The identification of patients at risk of CNS relapse remains inconclusive [23]; however, data from immunocompetent individuals suggests that advanced stage, elevated serum LDH and extranodal disease [93] and involvement of specific anatomical sites such as: testes [94,95], paranasal sinuses [96], paraspinal disease, breast [97], renal [90], epidural space [98] and bone [99,100], predict a higher likelihood of CNS relapse.

Both intrathecal and intravenous methotrexate have been used to prevent CNS disease. There are insufficient data to identify whether HIV-positive patients have a higher risk of CNS relapse independent of other criteria and thus such patients should be given CNS prophylaxis according to the same criteria as HIV negative patients. There is universal acceptance that all patients with Burkitt Lymphoma should receive specific protocols that include CNS directed therapy, which in the UK in most instances is R-CODOX-M/R-IVAC.

3.5.1 Recommendations for IT prophylaxis

Patients with DLBCL, considered to have a high risk of CNS relapse, should be given CNS prophylaxis (IT and/or IV methotrexate) according to the same criteria as HIV negative patients (level of evidence 1C).

Prophylactic intrathecal chemotherapy should be offered to all patients with Burkitt lymphoma (level of evidence IB).

3.6 Supportive care

Patients with a high tumour burden are at risk of developing tumour lysis syndrome (TLS). This can occur spontaneously or after commencement of chemotherapy (usually between 12 and 72 hours after). Patients thought to be at high risk of developing TLS include those with DLBCL who have an elevated LDH and bulky disease and those with BL with stage III/IV disease or an elevated LDH. These patients should receive aggressive treatment to prevent TLS, including adequate intravenous hydration and rasburicase. Those who do not meet the criteria for high-risk disease should also be adequately hydrated, although oral hydration and allopurinol may suffice [101].

The inclusion of prophylactic agents to reduce the incidence of infectious complications is common but details regarding this are discussed elsewhere. It is usual to give HIV-patients receiving chemotherapy prophylactic G-CSF to prevent or limit the duration of neutropenia.

3.7 Treatment of relapsed/refractory AIDS-related lymphoma

Treatment of refractory or relapsed DLBCL in the pre-HAART era was disappointing with few clinically useful responses [102-104]. In the HIV-negative setting, patients are treated with a more intensive second-line chemotherapy regimen. For those who respond, studies have shown that consolidation with high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) is the optimal therapy for relapsed NHL [105]. Since the introduction of concomitant HAART therapy, with the associated improvement in the immune function and haematological reserve, and better supportive care, a number of studies have confirmed that this strategy is both feasible and effective in the HIV setting [106-114].

Even in the HIV-negative setting, there is no standard second-line chemotherapy regimen but most contain platinum agents. Commonly used regimens include DHAP (dexamethasone, high-dose cytarabine and cisplatin) and ICE (ifosfamide, cisplatin and etoposide). This is usually combined with rituximab, although the value of rituximab in those who relapse early after or are refractory to upfront treatment with rituximab is less clear. Response rates to these second-line chemotherapy regimens in HIV-negative patients are around 60% [115]. Similar results have been achieved in HIV-positive patients [106].

Two large, retrospective, multi-centre studies performed by the European Group for Blood and Marrow Transplantation (EBMT) have confirmed the feasibility and efficacy of HDT and ASCT for HIV-positive patients that respond to second-line chemotherapy [116,117]. In one of these studies a comparative analysis was performed between 53 HIV-positive lymphoma patients and a matched cohort (66% non-Hodgkin and 34% Hodgkin lymphoma) of 53 HIV-negative patients [116]. The incidence of relapse, OS and PFS were similar in both cohorts. A higher non-relapse mortality within the first year after ASCT was observed in the HIV-positive group (8% vs 2%), predominantly because of early bacterial infections, although this was not statistically significant and did not influence survival. In the other study performed by the EBMT, the outcome of 68 patients from 20 institutions (median age, 41 years; range, 29–62 years) transplanted after 1999, for relapsed NHL (*n* = 50) or Hodgkin lymphoma (*n* = 18) was reported [117]. At the time of ASCT, 16 patients were in first CR; 44 patients were in second CR and beyond, PR, or chemotherapy-sensitive relapse; and 8 patients had chemotherapy-resistant disease. At a median follow-up of 32 months (range 2–81 months), PFS was 56%. Patients not in CR or with refractory disease at ASCT had a worse PFS (RR = 2.4 and 4.8, respectively) as is frequently reported in the HIV-negative setting. Thus, in the HAART era, HIV patients with chemosensitive relapsed ARL should be considered for ASCT according to the same criteria adopted for HIV-lymphoma patients.

3.7.1 Recommendations for patients with relapsed/refractory aggressive ARL

Patients deemed fit for intensive chemotherapy should receive a second-line chemotherapy regimen (level of evidence 1C) which maybe platinum containing (level of evidence 2C).

Those responding to second-line chemotherapy (CR or PR) should be considered for HDT with ASCT (level of evidence 1C).

3.8 Response evaluation and follow-up

Specific response criteria for NHL in HIV-positive patients have not been described, but the International Working Group response criteria defined for the general population are generally used and are shown in Table 3.8 [21]. Response to treatment is assessed by clinical evaluation, CT scanning and bone marrow biopsy (if the CT scan shows CR and BM was involved at diagnosis). It is usual to assess response half way through treatment, i.e. after 3–4 cycles of R-CHOP chemotherapy or 2 cycles of R-CODOX-M/IVAC. However, the role of ^{18}F-FDG PET scanning during therapy is less clear due to the high false positive rate [118] and is thus currently not recommended. At the end of treatment, in addition to the mid-treatment investigation, a ^{18}F-FDG PET scan is recommended as in the HIV-negative setting it has been shown to be superior to CT scanning in detecting residual disease with a very high negative predictive value [21]. These investigations should be performed at least 4–6 weeks after the last cycle of chemotherapy and 8–12 weeks after radiotherapy.

It should be noted that the role of ^{18}F-FDG PET scanning has been less well studied in HIV-positive patients and false-positive results due to HIV-related pathology are reported, resulting in a positive predictive values of <10%. Nonetheless, the negative-predictive value is high [35]. Therefore, re-biopsy of residual FDG-avid lesions post-therapy should always be considered. Those with persistent disease should be considered for salvage therapy, and those who have achieved a CR, observed.

The decision to offer consolidation radiotherapy should be made at presentation (i.e. to bulk disease or bony lesions) and not to residual FDG-avid lesions in those treated with curative intent, as PET-positive lesions may represent more widespread disease. RT may be offered to those with PET-positive lesion(s) and who are ineligible for salvage chemotherapy.

There are scant data regarding long-term follow up of survivors of lymphoma treatment in the HIV setting. However it is well described in the HIV negative setting that prior anthracyclines (e.g. doxorubicin) are associated with cardiomyopathy and heart failure. Although it is unclear if the incidence is higher in the HIV setting, patients with other cardiovascular risk factors (e.g. blood pressure, lipids, family history) may deserve greater surveillance.

Chemotherapy for lymphoma is associated with an increased risk of myelodysplasia and acute myeloid leukaemia arising some 2–7 years later, often with cytogenetic abnormalities of chromosomes 5, 7 or 12. Chemotherapy is also associated with an increased risk of second solid tumours, although previous radiotherapy is the greater risk factor. Other potential issues include endocrine and metabolic complications.

Follow up varies between centres but generally patients with aggressive histologies are seen every 3 months in the first year, 4–6 monthly for the second and third and thereafter 6 monthly until 5 years post treatment. Patients are then often discharged to primary care (having received an 'end-of-treatment summary') although data regarding long-term side effects in patients with HIV who have received treatment for lymphoma are scant. In light of this some patients continue to be monitored on an annual basis.

Table 3.8 Response assessment in patients with DLBCL

Response	Definition
CR	Complete clinical and radiological disappearance of disease. PET negative.
PR	≥50% decrease in diameter of up to 6 of the largest dominant masses. PET positivity in a previously involved site.
SD	Failure to attain CR/PR or PD
Relapsed or PD	Any new lesion or increase by ≥50% of a previously involved site.

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4.0 Primary central nervous system lymphoma (PCNSL)

4.1 Introduction

Primary central nervous system lymphoma (PCNSL) is defined as a non-Hodgkin's lymphoma (NHL) confined to the cranio-spinal axis without systemic involvement. It occurs more frequently in patients with both congenital and acquired immunodeficiency. Immunosuppression is a risk factor for the development of lymphoproliferative disorders. In HIV it is seen in patients with severe immunosuppression and the duration of severe immunosuppression. It can affect any part of the brain, leptomeninges, cranial nerves, eyes or spinal cord [1]. AIDS-related PCNSL occurs with a similar distribution across transmission risk groups and all ages, and is characteristically high-grade diffuse large B-cell or immunoblastic NHL [2]. Shortly after the introduction of highly active antiretroviral therapy (HAART), a decline in the incidence of PCNSL was recognized and a meta-analysis of 48 000 individuals confirmed this significant decrease [relative risk 0.42; 99% confidence interval (CI) 0.24–0.75] [3]. A subsequent study has shown that the incidence of PCL is lower in the HAART era (1.2 cases per 1000 patient-years; 95% CI 0.8–1.9) than in the pre-HAART era (3.0 cases per 1000 patient-years; 95% CI 2.1–4.0; $P<0.001$), and overall survival is longer (median survival 32 days, range 5–315 vs. 48 days, range 15–1136 days; log rank $P=0.03$) [4].

4.2 Diagnosis, staging and prognosis

Patients rarely present with B symptoms such as fever, weight loss, or night sweats that are commonly associated with other forms of NHL. PCNSL typically presents with a focal mass lesion in more than 50% of cases. In 248 immunocompetent patients, 43% had neuropsychiatric signs, 33% had increased intracranial pressure, 14% had seizures, and 4% had ocular symptoms at the time of presentation [3]. Examination includes full medical, neurological, slit lamp examination of the eye and neuropsychological assessment. Investigations including serum LDH, CSF analysis, radiology (MRI brain, CT CAP), bone marrow aspirate and trephine biopsy will help to support the diagnosis of PCNSL. Stereotactic brain biopsy is the only confirmatory test and this can be guided by PET scan. The presence of Epstein–Barr virus (EBV) in tumour cells is a universal feature of HIV-associated PCNSL but is not found in other PCNSLs [4,5]. In patients with HIV, computed tomography (CT) scans of PCNSL may show ring enhancement in as many as half the cases, whilst in immunocompetent patients with PCNSL the enhancement is almost always homogeneous [6,7]. Most commonly, PCNSL presents as diffuse and multifocal supratentorial brain masses. As a peculiarity of PCNSL, involvement of the vitreous, retina and optic nerves may be found in about 10–15% at presentation [8]. Lymphomatous infiltration of the leptomeninges or ependymal surfaces and radicular or plexus invasion may occur as well [9]. By systemic staging, occult systemic lymphoma may be detected in up to 8% of patients initially presenting with brain lymphoma. Therefore, bone marrow biopsy, CT scan of chest and abdomen, testicular ultrasound and careful physical examination to detect occult systemic lymphoma is recommended [10]. The diagnostic algorithm for the management of cerebral mass lesions in HIV-seropositive patients includes a 2-week trial of anti-toxoplasmosis therapy (sulphadiazine 1 g four times a day, pyrimethamine 75 mg once daily). Magnetic resonance imaging is the most sensitive radiological procedure: the densely cellular tumour appears as single (65%) or multiple lesions on nonenhanced T1-weighted

images, hyperintense tumour and oedema on T2 or FLAIR images and densely enhancing masses after administration of gadolinium. Fifty per cent or more of the lesions are in contact with the meninges, and meningeal enhancement appears in 10–20% [11].

4.3 Treatment of HIV associated primary cerebral lymphoma

The treatment of HIV associated primary cerebral lymphoma is poor with median survival reported rarely reported greater than 9 months. Primarily the reasons for this are due to the advanced stage disease at the time of presentation with low CD4 cell counts (typically below 100/μl) and poor performance status. Compared to immune competent patients the age of presentation tends to be younger, with worst performance status and higher LDH. Often the patients present with multifocal disease.

In the HIV population the incidence of PCNSL has fallen dramatically since the introduction HARRT [12,13]. In immune competent individuals the treatment of choice is chemotherapy with the anti-metabolites, methotrexate and cytarabine forming the backbone of the majority of PCNSL regimen and is the current regimen of choice for *de novo* immune competent patients [14] with PCNSL However, in the HIV population this is rarely feasible due to poor performance status and concerns over toxicity with the combination of two chemotherapeutic agents. Therefore single modality use of intravenous methotrexate is most the utilized treatment yielding median overall survival of 8–9 months in most small series of patients [15,16]. In these situations it is recommended to utilize growth factors such as GCSF to prevent enhanced haematological toxicity in this population. In patients with well-controlled HIV viral load and good performance status and in the absence of co-morbidities, ideally the treatment of choice would be combination therapy with a methotrexate and Ara C combination. In these case where treatment is tolerated and chemosensitive disease demonstrated, consolidation of an autologous stem transplant should be considered.

Because of the association with EBV and HIV-related PCNSL, investigators have tried to develop antiviral-based regimens including nucleoside analogues such as AZT and ganciclovir [17]. However, although ORR rates of 56% were reported, outcome measures remain disappointing with OS reported of 4 months [16], which is inferior to single agent methotrexate. In the future, further knowledge of the biological basis of EBV and its association with PCNSL may facilitate novel targeted approaches. The use of HAART is mandatory, and has been demonstrated in three small series to be correlated with enhanced OS [16,18,19]. Part of its effect maybe to induce restoration of an immune response to EBV. Therefore it is recommended to initiate HARRT to all newly diagnosed patients with HIV PCNSL. Newer antiviral agents with minimal drug–drug interaction may facilitate the ability to administer standard or intensive chemotherapy agents. Radiotherapy is a useful palliative treatment modality for control of symptoms or should be considered as an alternative treatment modality in those patients first line where the risks of toxicity from high dose intravenous agents are considered unacceptable.

4.4 Recommendations

We recommend that all patients with PCNSL should be started on HARRT if not already on it (level of evidence 1C).

We recommend that patients with an adequate performance status should be treated if possible, with high dose methotrexate containing chemotherapy regimen (level of evidence 1D).

We recommend that whole brain radiotherapy is a useful palliative treatment modality for control of symptoms or should be considered as an alternative treatment modality in those patients first line where the risks of toxicity from high dose intravenous agents is considered unacceptable (level of evidence 1C).

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5.0 Primary effusion lymphoma (PEL)

5.1 Introduction

Primary effusion lymphoma (PEL) is an unusual rare form (approximately 3%) of HIV-associated non-Hodgkin lymphoma. Patients with PEL are usually HIV-positive men and the presentation is unique in that growth in a liquid phase is observed in serous body cavities such the pleura, peritoneum and pericardial cavities without identifiable tumour masses or lymphadenopathy. The precise diagnosis rests on demonstrating the human herpes/human herpes virus 8 (HHV-8) in the malignant cells, which are characterized by distinct morphological appearance and the absence of typical mature pan B and T cell immune-histochemical markers. The prognosis of HIV-related PEL remains poor with a median survival reported in one large series of 6.2 months [1].

5.2 Pathogenesis

The pathogenesis of PEL is linked to the presence of HHV-8, which promotes tumorigenesis by enhanced proliferation and impaired apoptosis in cells with latent gene HHV-8 expression. Three latent gene products are latency-associated nuclear antigen-1 (LANA-1), viral cyclin (v-Cyc), and viral FLICE inhibitory protein (vFLIP). LANA-1 functions to tether the viral genome to the infected hosts cell's genome [2] and also promotes cell survival by, and transformation of, infected cells by interaction with the tumour suppressor gene P53 and retinoblastoma gene [3,4]. v-Cyc is a viral homologue of cyclin D and binds to cyclin dependent kinase 6 (cdk-6), which results in resistance to CDK inhibitors, progression through the cell cycle and uncontrollable proliferation [5]. Further proactivation of NF kappa B pathways by vFLIP and inhibition of apoptosis by blocking Fas-mediated caspase activation contributes to cellular transformation [6]. Another herpes virus, EBV, plays an unclear role in PEL pathogenesis. Studies of EBV gene expression indicated that a restricted latency pattern of expression with minimal transforming genes evident suggesting a supportive role of EBV in cellular transformation [7].

5.3 Presentation

Patients commonly present dyspnoea as a result of pleural or pericardial involvement or abdominal distension from peritoneal involvement. Due to poor survival with conventional therapy, frequent causes of death are related to progressive disease, opportunistic infection or other HIV-related complications.

5.4 Diagnosis

The diagnosis should be suspected in cases with the unique presentation of PEL with cytological analysis of the involved effusion fluid. The definitive diagnosis rests upon the morphological, immune phenotype and virological content of the affected tumour cells. Morphologically the cells are large, have round to irregular nuclei and conspicuous nucleoli, and may have the appearance of immunoblasts, plasmablasts and/or anaplastic forms [8]. Detection of evidence of viral infection is a *sine qua non* to make the diagnosis, and

although serological evidence of infection informs of previous infection, immunohistochemical stating for LANA-1 expression is the standard to detect HHV-8 in tumour samples. Quantitative measurements of HHV-8 viral load are available but no studies have yet demonstrated correlation of viral mass with prognosis or response to therapy. The immunophenotype of PEL cells display a 'null' lymphocyte phenotype with expression of CD45 but absence of characteristic B cell markers (CD19, CD20, CD79a) and T cell markers (CD3, CD4, CD8). The cells express activation markers (CD30, CD38, CD71, HLA DR) and plasma cell markers (CD138) [8]. The cells of are of B cell origin as evidenced by the presence of immunoglobulin gene rearrangements and somatic hypermutation [9]. Cytogenetic evaluation has revealed complex karyotypes but no recurrent chromosomal abnormalities [10]. The differential diagnosis is that of another NHL subtype associated with a lymphomatous effusion but the clinical appearance without solid LN masses and the requirement for HHV-8 evidence and typical immunophenotype should leave little room for error.

5.5 Prognosis and management

Due to the low incidence of the disease randomized clinical trials are not feasible and as such, there is no clear standard of care established to treat PEL. Since the widespread use of highly active retroviral therapy the morbidity and mortality associated with HIV infection has declined and in particular treatment results of HIV-associated lymphoma have improved. Unfortunately the results for HIV-associated PEL remain disappointing and no specific treatment regimen is currently recommended for PEL. There have been sporadic case reports of HAART-induced responses alone [11] and the use of HAART in any treatment regimen is recommended. In a single institution study [12], which included 11 cases of PEL, treatment with CHOP resulted in an overall response rate of 42% and median survival of 6 months despite standard concomitant HAART. In a further study by Boulanger [1] of 28 patients with PEL prognostic factors identified at the time of diagnosis by multivariate analysis identified two factors indicative of poor clinical outcome: poor performance status; and the absence of HAART before PEL diagnosis. Only rare cases of CHOP-induced remission have been reported in patients simultaneously treated with HAART [13,14]. Because of the induction NF-kB in PEL cell lines has led to the investigation of proteasome inhibition in NF-kB-driven haematological malignancies. Velcade has recently been approved for the use in multiple myeloma and would seem an attractive therapy for PEL because of its intrinsic biology. Further antiviral approaches have been tried and in one patient the combination of interferon-alpha and AZT has been used with success [15]. Current clinical trials by the NCI are utilizing a combination approach of antivirals, velcade and systemic chemotherapy. Further opportunities have proposed targeting latency phase genes such as LANA-1 using siRNAs to silence viral regulatory proteins and augmentation of host immunity against HHV-8.

5.6 Recommendations

Diagnosis criteria requirement:

Characteristic morphology, immunophenotype and demonstration of HHV-8 in tumour samples (level of evidence IIIB).

Treatment:

First line for PEL in HIV-positive individuals includes CHOP- like regimens. No comparative studies have been performed and there is no optimal gold standard therapy (level of evidence tbc [IIA, B?]).

Where possible, patients should be entered into clinical trials that are testing novel targeted approaches.

Chemotherapy regimens should be combined with HAART therapy (level of evidence IIIB).

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6.0 Plasmablastic lymphoma

6.1 Introduction

Plasmablastic lymphoma accounts for 2.6% of all HIV-related lymphomas [1]. In the original report 15/16 cases were HIV infected and had involvement of the oral cavity [2]. The disease can also occur in the non-HIV population particularly those on immunosuppression. There are three recognized subtypes of plasmablastic lymphoma. The first is plasmablastic lymphoma of the oral mucosa, which contains a monomorphic population of plasmablasts with minimal plasmacytic differentiation and usually found in the oral mucosa. The second type tends to have more plasmacytic differentiation and usually extra oral. The third type is plasmablastic lymphoma associated with Castleman's disease and is typically nodal or splenic. In WHO classification 2001 the tumour is a subtype of diffuse large B cell lymphoma (DLBCL). The majority of patients with PBL are men, particularly in the HIV population with a mean age of presentation of 39 years.

6.2 Morphology

These tumours need to be distinguished from the immunoblastic variant of DLBCL and body and extra cavity variants of primary effusion lymphoma (PEL), Burkitt lymphoma (BL) with plasmacytoid differentiation, and extramedullary plasmablastic secondary multiple myeloma. Advances in immunophenotyping have facilitated these distinctions based on the low or absent expression of leukocyte common antigen (CD45) or the B cell markers CD20, CD79a, and PAX5. The plasma cell markers VS38c, CD38, multiple myeloma oncogene-1 (mum-1) and CD138 (syndecan-1) are almost always expressed [3]. The tumour cells are nearly always EBV-positive and this may be demonstrated in its three latent forms by the use of fluorescent or chromogenic *in situ* hybridization and may be useful in distinguishing from plasmablastic multiple myeloma.

6.3 Pathogenesis

Based on immunohistochemical, molecular and genetic studies, PBL is thought to derive from post germinal centre terminally differentiated activated B cells. These cells have undergone class switching and somatic hypermutation. A recent study has demonstrated chromosomal rearrangements involving the cMyC oncogene and the immunoglobulin gene [4].

6.4 Clinical presentation

The disease is unique for its predilection to arise in the oral cavity of HIV-positive individuals. Extraoral involvement may occur with the most commonly affected sites being the gastrointestinal tract, lymph nodes and skin. Many (60%) patients present with advanced disease. In a series of 131 cases, affected patients had a median CD4 cell count of 173 cells/μL with presentation on average 5 years after the initial diagnosis of HIV. Interestingly most patients (>95%) presented with either stage I or IV disease.

6.5 Treatment

In the pre-HAART era prognosis was poor with a median survival of only 5 months. The use of HAART has improved overall survival for patients and is recommended. The use of chemotherapy is important in the initial therapy of PBL and patients who do not receive chemotherapy have a dismal prognosis with median survival of only 3 months [5]. CHOP-like treatments have been the standard of care but due to the disappointing long-term survival rates, more intensive regimens have been suggested such as HyperCVAD, or CODOX-M-IVAC. However, a recent review has not shown these higher intensity regimens to confer an overall survival advantage [6]. Despite good ORR to chemotherapy in the region of 70–80%, the median overall survival is 14 months with a 5-year survival OS of 31% [3]. PBL has a similar profile to that of non-germinal centre DLBCL and therefore targeting biological pathways such as NF-kB may have benefit. A case reported in a patient started on HAART and bortezomib displayed a rapid response after 4 cycles of therapy but unfortunately the case was complicated by fatal sepsis [7]. A further case reported skin regression while on velcade; however, the patient then relapsed early [8]. Early case reports are encouraging and may further yield better results when combined with chemotherapy in the future.

6.6 Recommendations

We recommend that patients should receive HAART with systemic anthracycline-containing chemotherapy as first-line therapy (level of evidence 1C).

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7.0 Cervical intraepithelial neoplasia (CIN) and cervical cancer

7.1 Introduction

In the UK, cervical cancer is the most common cancer in women aged below 35, and the 11th most common in women overall. Worldwide, however, cervical cancer is the second most common cancer in women. In 2009, there were 2747 new diagnoses of cervical cancer in the UK, and in 2008, there were 759 recorded deaths from this disease; around 7% of deaths were in women below the age of 35 [1]. Death rates from cervical cancer in the UK fell markedly by around 70% between 1979 and 2008; much of the reduction in deaths is attributable to cervical screening.

Almost all cases of invasive cancer are associated with infection with oncogenic types of human papilloma virus (HPV), particularly HPV 16 and 18 [2]. Invasive cancer is preceded by cervical intraepithelial neoplasia (CIN), which can be detected by cervical screening; around 75% of cases of cancer are potentially preventable by screening [1]. Cervical cancer is around twice as common in women who smoke [1]. Women who smoke should be encouraged to stop smoking; effective interventions include simple opportunistic advice, individual behavioural counselling or group behaviour therapy, telephone counselling, provision of self-help materials and pharmacotherapy with nicotine replacement, varenicline and bupropion [3].(***CHECK LEVEL GRADING IN BHIVA standards of care guidelines)

The incidence of some HIV-associated cancers, including Kaposi sarcoma and non-Hodgkin lymphoma has fallen markedly in populations who have been treated with antiretroviral therapy. In contrast, the incidence of cervical cancer has not changed significantly. There are a number of possible explanations for this observation. First, the differences in rates of decline of these cancers may reflect fundamental differences in their biology and association with different viral infections (HHV-8, EBV and HPV). Secondly, the increase in incidence of cervical cancer associated with HIV is much lower than the increased risk of lymphoma or Kaposi sarcoma, so that any changes in incidence of cervical cancer in the HAART era may be less evident. Finally, survival bias may mask an effect, i.e. the absence of a rise in incidence in an ageing population may in fact be evidence of an effect of antiretroviral therapy [4,5].

7.2 Screening for cervical cancer and pre-cancer

The UK cervical cancer screening programme has specific recommendations for screening and management of women with HIV infection [6], which are summarized in 7.6 Key recommendations below.

Women with HIV infection are more likely to have infection with HPV 16 or 18 [7,8]. Women with HIV infection also have a higher prevalence [9,10] and incidence [10,11] of CIN than HIV-negative women. There is some evidence that HIV-positive women are at increased risk of false negative cytology [12], although other studies have shown that cytology performed at 2-yearly intervals is sufficiently sensitive for cervical surveillance in women with HIV [13].

7.3 The effect of HAART on the natural history of CIN

In contrast to the relative lack of an effect of ART on the incidence of invasive cervical cancer, there is evidence from multiple cohort studies that ART is associated with a reduction in the incidence of CIN [4,5,14–19], although this finding is not universal [20–23]. Furthermore, the incidence of CIN is increased in women with lower CD4 cell counts, while higher CD4 cell counts are associated with a reduction in incidence and progression of CIN, and an increase in regression of disease [4,5,17,19]. The clinical significance of these findings is unclear. Whilst it is plausible that earlier initiation of ART may be associated with increased regression and a decreased incidence of CIN, at present the quality of the evidence does not permit a clear recommendation for earlier treatment in women with CIN to be made.

7.4 Diagnosis and management of CIN

Women with HIV and abnormal cytology should be managed according to the UK national guidelines [6]. Similarly women with HIV and histologically proven CIN 2/3 lesions should be treated and followed up according to the UK national guidelines [6]. These do not mandate a specific treatment modality for CIN 2/3 although various types of excision techniques are most commonly used. In women with HIV infection, persistence and recurrence of CIN 2/3 after treatment are more common than in HIV-negative women [24–30]. Risk factors for treatment failure in HIV- positive women include CD4 <200 cells/µL [24–26,28,31,32], higher HIV viral load [27,31], and non-use of HAART [24,26]. Compromised margins on the excisional specimen are seen frequently in women with HIV and are also a risk factor for treatment failure [24,26,27,31–33]. Few studies have looked at the relationship of surgical procedure to treatment failure in women with HIV infection, but one study found use of LLETZ (RR 3.38, 95% CI 1.55–7.39) compared to cold knife cone to be a risk factor [31]. No specific information is available for late adverse obstetric outcomes in women with HIV treated for CIN.

7.5 Diagnosis, staging, management and prognosis of cervical cancer

Women with HIV and invasive cervical cancer should be managed in the same manner as HIV-negative women according to UK national guidelines [34]. Diagnosis is based on histopathological examination of cervical biopsies, and clinical staging uses the FIGO criteria. Radiological assessment of patients with cervical carcinoma is an essential part of the staging process. In general, MRI is used for clinical staging unless there are contraindications to MRI, and PET or PET-CT may be used additionally for the detection of metastatic lymphadenopathy.

In general, surgery is used as treatment for FIGO IA1, IA2 and IB1 disease, whereas concurrent chemoradiotherapy with platinum-based chemotherapy is recommended for treatment of IB2, IIA, IIB, IIIA and IVA disease. There is very little published clinical data on women with HIV and cervical cancer, and essentially all of this is reported from the developing world. Women with HIV infection and cervical cancer present at a younger age than HIV-negative women [35,36], whereas data are conflicting whether women with HIV present with more advanced disease [35,36]. Only one series is reported from the HAART era, and where women were treated with chemoradiotherapy [36]. That series showed that 90% of HIV-negative women completed radiotherapy compared to 80% of HIV-positive

women, and that 75% of HIV-negative women completed ≥4 weeks of platinum-based therapy compared to 53% of HIV-positive women. However, completion rates of chemotherapy were not related to receiving HAART or not, but were associated with higher CD4 cell counts (median 416 vs 311 cells/μL) [36].

7.6 Key recommendations

All women newly diagnosed with HIV should have cervical surveillance performed by, or in conjunction with, the medical team managing their HIV infection (level of evidence 1B). An initial colposcopy and annual cytology should be performed if resources permit (level of evidence 2C).

Subsequent colposcopy for cytological abnormality should follow UK national guidelines, and the age range screened should be the same as for HIV-negative women (level of evidence 1B).

CIN 2/3 (HSIL) should be managed according to UK national guidelines. Lesions less severe than CIN 2 should probably not be treated according to CIN 2/3 recommendations, as these low-grade lesions represent persistent HPV infection of the cervix rather than pre-malignancy (level of evidence 2B).

Women with HIV and CIN 2/3 treated by excisional procedures have a significantly higher treatment failure rate than HIV-negative women. A number of studies show such relapse is less frequent in the presence of HAART or higher CD4 cell counts or undetectable viral load. Multidisciplinary management of such women is thus recommended (GPP).

Women with HIV who have invasive cervical cancer should be managed in the same way as HIV-negative women according to UK national guidelines, again within a multidisciplinary team framework (level of evidence 1B).

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8.0 Anal cancer

8.1 Introduction

The updated published UK guidelines for the management of sexual and reproductive health (SRH) of people living with HIV infection, produced jointly by BHIVA, BASHH and FFPRHC, includes advice on anal cancer in HIV infection (available online at www.bhiva.org). The key points and recommendations are included below [1].

8.1.1 Key recommendations of BHIVA, BASHH and FFPRHC 2008 guidelines on anal cancer in HIV

All major HIV units should develop clinical guidelines for the management of suspected anal cancer and pre-cancer.

All major HIV units should develop either local clinical expertise or referral pathways for suspected anal cancer and pre-cancer.

The role of annual anal cytology and anoscopy is not yet proven, however, patients should be encouraged to check and report any lumps noticed in the anal canal.

8.1.2 Key recommendations of NICE 2004 guidelines on anal cancer

In addition, the management of anal cancer is included in the updated Guidance on Cancer Services Improving Outcomes in Colorectal Cancers published by NICE (National Institute for Health and Clinical Excellence) [2]. The recommendations make no reference to HIV but are included below.

Anal cancer is a rare disease and specific expertise is important to optimise outcomes for patients. All patients with anal cancer, including those who have undergone local excision, should therefore be referred to multidisciplinary anal cancer teams that can provide specialist management.

Patients for whom curative treatment is likely to be appropriate should have a computed tomography (CT) scan of the abdomen and pelvis or pelvic magnetic resonance imaging (MRI).

Primary treatment: Concurrent chemoradiotherapy, using mitomycin C, 5-fluorouracil and radiation, is appropriate for most patients. Other forms of treatment, such as surgical excision, may be considered by anal cancer multidisciplinary teams (MDTs), but surgery is usually reserved for salvage. There are still some areas of uncertainty about optimum treatment, and eligible patients should be encouraged to participate in trials such as the Cancer Research UK (CRUK) ACT 2 trial.

Management of relapse: All patients with suspected or confirmed relapse should be discussed by the anal cancer MDT. Those with confirmed loco-regional recurrence should undergo cross-sectional imaging and all treatment options, including surgery, should be considered by the MDT. Palliative radiotherapy, chemotherapy and palliative care should be discussed with

patients who have metastatic disease or who are not sufficiently fit to undergo potentially curative treatment.

The incidence of anal cancer in people living with HIV is up to 40 times higher compared with the general population [3] and it occurs at a much younger age [4-7]. The highest risk is in HIV-positive men who have sex with men (MSM) who have an incidence of 70–100 per 100,000 person years (PY) compared with 35 per 100,000 PY in HIV-negative MSM [8]. Recent studies confirmed the high incidence in HIV-positive MSM, other HIV-positive men and in HIV-positive women [9,10]. Importantly, the incidence of anal cancer appears to have risen with the widespread use of HAART [7,9,11-17].

It is believed that the pathogenesis of invasive anal cancer resembles that of cervical cancer with human papilloma virus (HPV) infection leading to anal intraepithelial neoplasia (AIN) and ensuing progression of low- to high-grade dysplasia and subsequently invasive cancer [4,18-20]. This pathogenetic model suggests a role for anal screening by a combination of cytology and high-resolution anoscopy followed by local ablative therapy of AIN. However, as noted in the 2008 BHIVA, BASHH and FFPRHC guidelines, the role of anal screening is not yet proven [1,20,21]. Whilst some centres have instituted screening pilots [22,23], the cost effectiveness analyses have produced both positive and negative results [24-29].

8.2 Diagnosis

The presentation of anal cancer can vary from rectal bleeding and anal pain to features of incontinence if the anal sphincters are affected, with some patients being asymptomatic [4]. Many comparative series have shown that people living with HIV who develop anal cancer are younger than HIV negative individuals with anal cancer [30-37]. However most comparisons suggest that there is no difference in tumour stage at presentation [30-40]. Since the prognosis of early stage anal cancer is better and late presentation may occur if anal symptoms are erroneously attributed to warts and haemorrhoids. We recommend the examination under anaesthetic (EUA) of the anal canal and rectum with biopsy in all suspected cases (level of evidence 1D).

8.3 Staging

We recommend that staging for anal cancer following EUA and biopsy, includes computerised tomography (CT) of the chest, abdomen and pelvis and MRI of the pelvis in order to assess regional lymph nodes and tumour extension [2] (level of evidence 1B). The American Joint Committee on Cancer (AJCC) TNM (tumour, node and metastasis) staging is used for anal cancer (Table 8.1) [41]. The stages are also grouped as 0–IV as shown below. Positron emission tomography (PET) imaging with [^{18}F] fluorodeoxyglucose may have a greater accuracy in identifying inguinal nodal involvement by anal cancer and has been used in HIV-positive patients with anal cancer but is not currently recommended as routine staging as experience is limited and false-positive rates are higher in people living with HIV [42-47]. Where doubt exists, lymph node sampling under radiological control is the optimal approach. Although squamous

cell carcinoma antigen (SCC) is a tumour marker expressed by anal cancers, its use in the diagnosis and follow-up of anal cancer is yet to be established [46].

Table 8.1: TNM staging for anal cancer

Primary tumour (T)	**Regional lymph nodes (N)**	**Distant metastasis (M)**
Tx Primary tumour cannot be assessed	Nx Regional lymph nodes cannot be assessed	Mx Distant metastasis cannot be assessed
T0 No evidence of primary tumour	N0 No regional lymph node metastasis	M0 No distant metastasis
Tis Carcinoma *in situ*	N1 Metastasis in perirectal lymph node(s)	M1 Distant metastasis
T1 Tumour >2cm or less	N2 Metastasis in unilateral iliac or inguinal lymph node(s)	
T2 Tumour >2cm but <5cm in greatest dimension	N3 Metastasis in perirectal and inguinal lymph nodes, bilateral internal iliac or inguinal lymph nodes	
T3 Tumour >5cm in greatest dimension		
T4 Tumour of any size invading adjacent organs e.g. vagina, bladder		

Stage grouping

The TNM descriptions can be grouped together into a set of stages, from Stage 0 to Stage IV as shown below:

Stage 0: Tis, N0, M0: Stage 0: carcinoma *in situ*.

Stage I: T1, N0, M0: tumour <2 cm in size.

Stage II: T2 or 3, N0, M0: tumour >2 cm in size.

Stage IIIA: *(*T1–3, N1, M0) or *(*T4, N0, M0): any size and either has spread to the lymph nodes around the rectum (N1), or has grown into nearby organs (T4), such as the vagina or the bladder without spreading to nearby lymph nodes.

Stage IIIB: *(*T4, N1, M0), or *(*Any T, N2-3, M0): the cancer has grown into nearby organs, such as the vagina or the bladder, and has also spread to lymph nodes around the rectum, or has spread to lymph nodes in the groin, with or without spread to lymph nodes around the rectum.

Stage IV: Any T, Any N, M1: spread to distant organs or tissues.

8.4 Management

The management of anal cancer in HIV patients requires a multidisciplinary team (MDT) approach involving oncologists, HIV physicians, surgeons, radiologists, histopathologists and palliative care specialists. In line with the 2004 NICE guidelines, we recommend that the management of HIV patients with anal cancer is in specialized centres where there is MDT experience in order to ensure the optimal outcomes [2] (level of evidence 1C). We suggest that centres caring for these patients should be able to provide high-resolution anoscopy services (level of evidence 2D).

8.4.1 First-line treatment for anal cancer

The first-line of treatment for anal cancer is concurrent chemoradiotherapy (CRT), which has been shown to achieve local control and sphincter preservation. Randomized controlled studies have established the superiority of CRT with 5-fluorouracil and mitomycin C and no other CRT regimen has been shown to be superior [48-52] (level of evidence 1A). There is consensus now that this CRT regime can be safely used for HIV patients and that outcomes are similar [30-35,38-40,53-55]. CRT generally has involved 5-fluorouracil and mitomycin C chemotherapy and concomitant radical radiotherapy to the pelvis (38–51Gy in 20–30 fractions), with most patients receiving a perineal boost (10–18Gy). Intensity-modulated radiation therapy (IMRT) has recently been used to achieve high doses of radiation with minimal impact to surrounding tissue so as to reduce the toxicity. This has been evaluated in anal cancer patients including HIV patients with decreased dermatological and gastrointestinal toxicity with good tolerance and this may become the standard of care in CRT for anal cancer [56-59].

8.4.2 Benefit of adding antiretrovirals to anal cancer treatment

The most common grade 3–4 toxicities of CRT are haematological, gastrointestinal and skin and some series have found that these are more common in patients with lower CD4 cell counts [60-62] although this is not a universal finding [40,53]. Whilst HAART has not reduced the incidence of anal cancer, the toxicity of CRT with HAART in more recent series, appears to have diminished somewhat [33,35,40,53,63-65]. Moreover, there has been a significant improvement in the overall survival from anal cancer diagnosis since the introduction of HAART; the 5-year overall survival has risen from 38% in the pre-HAART era to 68% in modern times [53]. In addition CRT is associated with a significant and prolonged decline in CD4 cell count even when concomitant HAART is prescribed [53,66]. On account of the apparent reduction in treatment-related toxicity and the decline in CD4 cell count we recommend that all people living with HIV who are to be treated with CRT should start HAART (level of evidence 1C) and opportunistic infection prophylaxis (level of evidence 1D).

8.4.3 Best treatment of relapse of anal cancer

All patients with confirmed or suspected recurrence should be discussed in the MDT meeting. In the general population, 22–25% of patients with anal cancer develop persisting residual primary disease or loco-regional recurrence following CRT [48,67]. Both residual primary disease and local recurrence after CRT are usually managed by salvage surgery, involving abdominoperineal excision of rectum and anal canal with a pedicle flap to assist perineal healing and the formation of a colostomy [68]. An APR may involve reconstruction surgery in conjunction with plastic surgeons for a muscle flap. The morbidity of APR can be considerable

and prolonged with delayed wound healing or dehiscence of the perineal wound [69]. Survival at 5 years following salvage surgery varies greatly between series, ranging from 29% to 61% [68,70-73]. Salvage surgery may be appropriate for people living with HIV who experience loco-regional disease persistence or relapse following CRT (level of evidence 2D) although experience in this population is limited [69]. In one series of salvage surgery, HIV seropositive status was not associated with poorer outcome [70] although delayed healing was reported in another series (ref tbc).

Patients with metastatic disease or local relapse following salvage surgery may be considered for palliative chemotherapy; however, responses are rarely complete and usually of short duration [46], so best supportive care may be more appropriate (level of evidence 2D).

8.4.4 Best response evaluation and follow up in anal cancer

Response to CRT should be assessed at 6–8 weeks after completion of CRT. Clinical evaluation, MRI imaging of the pelvis and EUA is usually performed. Earlier evaluation may underestimate response rates and indeed in the ACT II trial (which excluded people living with HIV) 29% of patients who had not achieved a complete response (CR) at 11 weeks after CRT subsequently achieved CR at 26 weeks [74]. Hence residual disease should be confirmed histologically. Follow-up protocols for the general population suggest clinical evaluation and review every 3–6 months for 2 years and every 6–12 months up to 5 years [46]. We suggest a similar approach in people living with HIV (level of evidence 2D) and advocate surveillance for AIN by HRA (level of evidence 2D).

8.5 Summary of guidance

We recommend the examination under anaesthetic (EUA) of the anal canal and rectum with biopsy in all suspected cases (level of evidence 1D).

We recommend that staging for anal cancer following EUA and biopsy, includes computerised tomography (CT) of the chest, abdomen and pelvis and MRI of the pelvis in order to assess regional lymph nodes and tumour extension [2] (level of evidence 1B).

We recommend that the management of HIV patients with anal cancer is in specialized centres where there is MDT experience in order to ensure the optimal outcomes [2] (level of evidence 1C).

We suggest that centres caring for these patients should be able to provide high-resolution anoscopy services (level of evidence 2D).

We recommend CRT with 5-fluorouracil and mitomycin C (level of evidence 1A).

We recommend that all people living with HIV who are to be treated with CRT should start HAART (level of evidence 1C) and opportunistic infection prophylaxis (level of evidence 1D).

We suggest that salvage surgery may be appropriate for people living with HIV who experience loco-regional disease persistence or relapse following CRT (level of evidence 2D).

We suggest that best supportive care may be more appropriate for patients with metastatic disease or local relapse following salvage surgery (level of evidence 2D).

We suggest a similar approach in people living with HIV (level of evidence 2D) and advocate surveillance for AIN by HRA (level of evidence 2D).

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9.0 Hodgkin Lymphoma (HL)

9.1 Introduction

Hodgkin lymphoma (HL) is one of the commonest tumours amongst the non-AIDS-defining malignancies (non-ADM) [1,2] with a 10- to 20-fold increased incidence in HIV patients in comparison with the HIV-negative population [1,3-6]. Conflicting results have been reported regarding the incidence of HL after the advent of highly active antiretroviral therapy (HAART): some authors have reported a slight increase in HL incidence [6], whereas others have not detected any difference in the incidence of HL in the pre-HAART and post-HAART eras [7,8].

HL in HIV patients tends to present more frequently in advanced stage at diagnosis, with extra-nodal involvement, especially bone marrow infiltration, and with a higher proportion of patients with B symptoms and poor performance status than in the general population [9-12]. From a histological point of view, HL in HIV patients is characterized by a predominance of the mixed cellularity (MC) and lymphocyte depleted (LD) subtypes, as opposed to nodular sclerosis (NS) [5,9-11,13,14], and by a higher percentage of EBV positivity [9,11].

The prognosis of HIV-HL in the pre-HAART era was considerably worse than in HIV-negative patients, with complete remission (CR) rates ranging from 44% to 65% [9,13,15,16], and median overall survival (OS) of about 18 months [9,15,16]. However, the outcome of HIV patients with HL has dramatically improved after the introduction of HAART; the CR rate, OS and disease-free survival (DFS) approach those seen in the general population [17-19].

9.2 Diagnosis, staging, prognostic factors

The diagnosis of HL, as that of any other lymphoid malignancy, should be based on a tissue sample biopsy, rather than on a cytological sample. Samples should be stained for CD20, CD3, CD15, CD30, BCL-2 and LMP-1 proteins.

Following the confirmation of diagnosis, patients should undergo a series of investigations (which include blood tests, whole body FDG-PET/CT scan and unilateral bone marrow biopsy) to assess the extension of the disease (see **Table** 9.1). Whereas a bone marrow biopsy is not necessary in all HIV-negative patients with HL, the higher proportion of bone marrow involvement in the HIV population [9,15] makes it mandatory. The above-mentioned investigations allow staging of the disease according to the Ann Arbor classification/Cotswolds modification [20] (see **Table 9.2**).

Table 9.1 Baseline investigations in HIV-associated HL

Haematology: FBC, reticulocyte count, ESR, blood group & screen.
Serum chemistry: U & E, albumin, calcium, phosphate, liver function, LDH, 2microglobulin, urate, CRP.
Virology: HbsAg, HbsAb, HepB core, anti HCV IgG, CMV IgG

ECG
Unilateral bone marrow (BM) biopsy and aspirate
Whole body FDG-PET/CT scan
Other investigations if clinically indicated (MRI, MUGA, ECHO)

Table 9.2 Ann Arbor classification/Cotswolds modification for staging HIV-associated HL

Stage I	Involvement of a single lymph node group or lymphoid structure
Stage II	Involvement of two or more lymph node groups on the same side of the diaphragm
Stage III	Involvement of lymph node groups on both sides of the diaphragm
Stage IV	Involvement of extra-nodal site(s) beyond those designated 'E'
X:	*Bulky disease: >10 cm or >1/3 widening of the mediastinum at T5–6*
E:	**Extra-nodal extension contiguous or proximal to known nodal site of disease or single isolated site of extra-nodal disease**
A/B:	*Absence/presence of B symptoms (weight loss >10%, fever, drenching night sweats)*

A prognostic score, which predicts both freedom from progression (FFP) and OS, has been defined for HIV-negative patients with advanced HL at diagnosis [21] (see **Table 9.3**). The applicability of the International Prognostic Score (IPS) in HIV patients was reported in a series of patients treated with Stanford V chemotherapy, in which the IPS was the only variable predictive for OS in the multivariate analysis. The IPS also predicted for FFP and CR rate [22]. Other prognostic markers that have been reported to have an impact on the outcome of HIV-HL patients include some predictive factors related to characteristics of the lymphoma, such as age, stage and responsiveness to therapy [12,23] and others associated with the HIV infection and/or its treatment [12,16,23-25]. Histological subtypes have been associated with prognosis in the HIV population in some studies [24] but not in others [23].

Table 9.3 International prognostic score (IPS) Hasenclever Index for Hodgkin lymphoma

Male sex
Age >45 years
Stage IV
Albumin level <4 g/dL
Hb < 10.5 g/dL

Lymphocyte count <8% or <0.6 x 10^9/L
Leukocyte count ≥15 x 10^9/L

9.3 Do antiretrovirals reduce the risk of HL?

Hodgkin lymphoma (HL) is one of the commonest non-AIDS-defining malignancies (NADMs) with age-adjusted incidence rates remaining 5–15-fold higher than in the general population. Despite the reduction in the incidence of ADMs since the advent of HAART, several large cohort studies have shown no fall in incidence rates of HL pre- and post-HAART [26-28], with some studies even showing increased incidence rates of HL immediately post HAART initiation [29].

The relationship between the incidence of HL and CD4 cell counts is complex. HL occurs most commonly at CD4 cell counts below 200 cells/µL [17,30]. However, there is ongoing risk of developing HL while on HAART despite an adequate CD4 cell count [26-28,30,31]. Furthermore, HL incidence rates are actually higher in the first few months after starting HAART [30-32]. Several cohort studies have also shown that drops in the CD4 count or CD4:CD8 ratio in the year prior to HL diagnosis may herald the advent of disease [27,28,33]. In contrast, viral load has not been shown to relate to incidence rates [26,30,31].

9.4. What is the best treatment for HL?

No randomized studies have addressed the question of the best chemotherapy regimen for patients with HL and HIV infection. The available data, especially in the pre-HAART era, is derived mainly from non-randomized studies or case series. There has been a growing tendency, since the advent of HAART, to treat patients with HIV and lymphoma with the same chemotherapy protocols used in the general population. Hence the recommendations on the treatment of HIV-HL are based on data extrapolated from studies performed in immunocompetent patients. Nevertheless, a significant difference in the management of HIV-positive patients with HL is that risk-adapted strategies are less commonly used. This is due to the smaller proportion of patients with good-risk disease in HIV-positive patients and the perceived higher risk because of HIV infection.

ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) remains, in most parts of the world, the standard chemotherapy regimen for patients with HL. The number of cycles and the addition of radiotherapy (RT) depends on the stage and risk factors of the disease (see Table 9.4 and

Table 9.5). Thus, in patients with early favourable stage HL, a short course of chemotherapy followed by involved-field (IF) RT is considered standard [34]. Recently, the German Hodgkin Study Group (GHSG) demonstrated in the randomized HD10 trial that ABVD x2 + 20Gy IF-RT results in a comparable freedom from treatment-failure (FFTF) and overall survival (OS) to ABVD x4 + 30Gy with less toxicity [35]. The results of the RAPID trial, only presented in abstract form, suggest that in patients with early stage HL (defined as stage IA–IIA without bulky

mediastinal disease, although bulky disease in other areas was allowed) with a negative FDG-PET after 3 cycles of ABVD, the addition of RT does not improve the outcome [36].

A recently published study reported on a small sub-group of HIV seropositive patients with early favourable stage HL who were treated according to a prospective stage- and risk-adapted strategy. Patients with early favourable stage HL received ABVD x2-4 + 30Gy IFRT. The complete remission (CR)/CR uncertain (CRu) rate was 96%, with a 2-year progression-free survival (PFS) of 100% and a 2-year OS of 96% [37]. Of note, 4 of 23 patients in this group were 'over-treated' (either by receiving BEACOPP instead of ABVD or by receiving more cycles than the protocol mandated). The transplant-related mortality (TRM) in this good-risk group was 4%.

With regards to the management of early unfavourable/advanced stage patients in the general population, the introduction of more intensive chemotherapies which result in higher response rates with significantly more toxicity, such as Stanford V (mechlorethamine, doxorubicin, vinblastine, prednisone, vincristine, bleomycin, etoposide), BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) and escalated BEACOPP, has led to some controversy on the treatment of these patients. The German HD11 study for patients with early unfavourable HL demonstrated that ABVD x4 + 30Gy resulted in a similar outcome, with less toxicity, than BEACOPP x4 + 30Gy [38]. The UK NCRN trial randomized patients with advanced-stage HL to ABVD *versus* Stanford V and demonstrated no significant differences in terms of PFS and OS [39]. An Italian randomized study compared ABVD x6-8 with BEACOPP (4 escalated + 4 baseline) in patients with advanced stage HL or high-risk (according to Hasenclever score) early stage HL and showed that whereas BEACOPP resulted in a superior freedom-from-progression than ABVD (85% vs 73%, respectively, at 7 years, P=0.004), this was not translated into a superior OS (7-year OS: 89% vs 84%) as patients who failed ABVD could be rescued with second-line chemotherapy followed by high-dose chemotherapy with autologous stem cell rescue (HDT-ASCR) [40]. Another randomized study, only presented in abstract form, confirms these results [41], as does as a recent meta-analysis [42]. In most of the studies of advanced stage HL RT is given to residual masses or sites of bulky disease at diagnosis. Ongoing studies are assessing the role of FDG-PET to enable omission of the RT.

One large published series describing HIV patients treated with ABVD in the HAART era included 62 patients with advanced-stage HL and reported a CR rate of 87% with a 5-year event-free survival (EFS) and 5-year OS of 71% and 76%, respectively [43]. A recent study compared the outcome of patients with HL treated with ABVD according to their serological status and demonstrated comparable results in terms of CR/CRu, EFS, disease-free survival (DFS) and OS for patients with and without HIV infection (table 2)[17]. The analysis revealed no significant difference in response rate, EFS, DFS or OS between 93 HIV seropositive patients and 131 seronegative patients with HL, supporting the treatment of HIV-positive patients with HL with the same schedules as in HIV-negative patients. In this study, 1 of 93 HIV-positive patients died of neutropenic sepsis with a further patient dying of an opportunistic infection 1 year after finishing chemotherapy.

There have not been studies comparing ABVD with more intensive regimens in the setting of HIV infection, but several phase II studies have reported on the efficacy and toxicity of intensive regimens in this population. Spina *et al*. published results on 59 patients treated with the Stanford V chemotherapy regimen with G-CSF support and concomitant HAART. One-third of the patients could not complete the 12-week treatment plan and 31% required a dose reduction, with considerable myelotoxicity and non-haematological toxicity. CR was achieved in 81% of the patients and after a median follow-up of only 17 months, the 3-year DFS was 68% and 3-year OS 51% [44]. A multicentre pilot study reported the use of the intensive BEACOPP chemotherapy in HIV positive patients with HL. Twelve patients were included in this study, which started in the pre-HAART era. Toxicity was considerable, with 4/12 discontinuing treatment, due to OI (two patients) and prolonged neutropenia (two patients). Grade 3-4 neutropenia was seen in 75% of patients, with six episodes of grade 3–4 infection. Of note, only two patients received HAART during chemotherapy, three patients received zidovudine monotherapy and G-CSF was optional, given in only 54% of the cycles; all these factors most likely contributing to the very significant toxicity reported in this study [45]. In contrast, in the above-mentioned stage-adapted study, 94% of patients received HAART during chemotherapy and G-CSF was recommended in all those receiving BEACOPP. Patients with early unfavourable HL (13% of the study population) received BEACOPP x4 or ABVD x4 + 30 Gy IF-RT, whereas those with advanced stage received BEACOPP x6–8. The CR/CRu rate was 100% and 86% for the early-unfavourable and the advanced stage groups respectively, and the 2-year PFS was 88% for both groups. Treatment related mortality was 0% in the early-unfavourable group and 6% in the advanced-stage group [37].

9.4.1 Recommendations

Early-favourable HL: ABVD x2–4 + IFRT 20-30 Gy (level of evidence 1B).

Early-unfavourable HL: ABVD x4 + IFRT 30 Gy (level of evidence 1B).

Advanced stage HL: ABVD x6–8 +/- RT (level of evidence 1B).

9.5. What is the benefit of adding ARVs to chemotherapy in HL?

Prior to HAART, the prognosis of HIV-HL was significantly worse than that of the HIV-negative population with reduced CR rates ranging from 44 to 65% [46-48] and median OS of about 18 months. Since HAART, the outcomes for patients with HIV-HL have dramatically improved with CR rates of 70–80% and EFS that are similar to the HIV negative population [17,19]. Moreover, in recent studies, 5-year OS rates approach that of the HIV-negative population [17-19]. Higher CD4 cell counts, HL stage appropriate therapy and HAART are key factors that correlate with these improved outcomes [49].

Although HAART and ABVD can be safely co-administered [17-19], patients remain at increased risk for treatment-related toxicities [19]. Similarly, drug–drug interactions between chemotherapy and specific types of HAART may drive adverse outcomes [19,50-53]. Clinically important adverse events such as additive vinblastine-mediated neurotoxicity and neutropenia in the presence of ritonavir have been described [50,51]. Some of these adverse events, such as

increased neutropenia, can cause delays in the chemotherapy schedule thereby compromising CR rates [51].

9.5.1 Recommendations

Patients should receive HAART during chemotherapy (level of evidence 2A).

Avoid PI/ritonavir-boosted regimens (level of evidence 1D).

9.6 What is the benefit of adding rituximab to chemotherapy in HL?

Once again the addition of rituximab to ABVD chemotherapy has been explored mostly in the setting of immunocompetent patients, with no studies in people living with HIV. Rituximab has demonstrated single-agent activity in HL, in spite of the fact that only 20–30% of classical HL expresses CD20. The depletion of reactive B-lymphocytes from the inflammatory background and the killing of clonotypic circulating B-cells have been hypothesized to explain rituximab activity in classical HL. A few phase II studies in HIV-negative patients have demonstrated the safety of the combination of rituximab with ABVD and its efficacy (CR/CRu rates: 81–93%; 3–5 year EFS: 83% and 5-year OS: 96%). These results are still very preliminary and several randomized studies are comparing chemotherapy (ABVD or BEACOPP) with and without rituximab.

9.7 What is the best treatment in second line for HL?

The standard strategy in good performance status immunocompetent patients with relapsed/refractory HL consists of inducing a response with salvage chemotherapy and consolidating it with high-dose therapy with autologous stem cell rescue (HDT/ASCR). This is based on two old randomized studies demonstrating the superiority of HDT/ASCR over only chemotherapy [54,55]. However, no randomized studies have compared different salvage regimens, and a number of phase II studies support the use of different regimes, with no evidence of superiority of one over the others. The most commonly used regimens are ESHAP, DHAP, MINE, IGEV, GEM-P.

No series has been published specifically on the treatment of relapsed/refractory HL in HIV patients. Thus recommendations are based on small studies of HDT/ASCR. As in the general population, the salvage protocols used vary and include ABVD, MOPP, CMOPP-ABV, MOPP/ABV, COPP-ABV, BEACOPP, vinorelbine, ESHAP, MINE, ifosfamide-VP16, ifosfamide-VP16-mitoxantrone and RT [25,56-58].

Several retrospective and prospective small pilot studies have demonstrated the feasibility of HDT/ASCR in patients with HIV and lymphoma [57,59], leading to the design of multicentre prospective studies aiming at confirming these results. Thus, the AIDS Malignancy Consortium Study 020 included 27 HIV patients with relapsed lymphoma, of whom 20 (5 with HL) received HDT/ASCR with dose-reduced busulfan-cyclophosphamide as the conditioning regimen [60]. There were only six episodes of febrile neutropenia and one treatment-related death due to veno-occlusive disease. CMV infection was demonstrated in four patients. Another prospective study by the Italian Cooperative Group on AIDS and Tumours (GICAT) recruited 50 patients [59].

Only 27 (including eight HL) patients actually received HDT/ASCR with no treatment-related deaths nor associated with infections. Four-year PFS and OS for the entire population was 49% and 50%, respectively, whereas it was 76% and 75% for those who actually received HDT/ASCR. A large retrospective registry matched-cohort study has demonstrated that the outcomes of patients with HIV infection who receive HDT/ASCR for relapsed/refractory lymphoma are comparable to those seen in HIV-negative patients [61]. At 30 months the PFS and OS for HIV-positive patients was 61%, whereas the corresponding figures for the control population were 61% and 70%, respectively (*P*=NS both for PFS and for OS).

9.7.1 Recommendations

Fit patients with relapsed/refractory HL should receive salvage chemotherapy and, if the disease proves to be chemosensitive, consolidate the response with HDT/ASCR (level of evidence 1B).

9.8 What is the benefit of adding opportunistic infection prophylaxis in HL

While there is no direct evidence to support opportunistic prophylaxis specifically in HL, prophylaxis is nevertheless recommended for PCP, MAI and fungal as in other HIV-related lymphomas [62].

9.8.1 Recommendations

PCP, MAI and fungal prophylaxis is recommended (level of evidence 1D).

9.9 What is the best response evaluation and follow-up in HL

No specific response criteria for HL in patients living with HIV have been described, so the response criteria defined for the general population should be used [63,64]. These guidelines were initially developed for patients with non-Hodgkin lymphoma (NHL) and were subsequently reviewed and modified to include HL, amongst other modifications. One of the important modifications is the recommendation for FDG-PET scanning both at baseline and for the assessment of response in HL. Interpretation of FDG-PET in patients with HIV infection should be done with caution as increased FDG uptake is detected in those with unsuppressed HIV viral loads [65,66]. However, in the absence of specific data on the applicability of FDG-PET scanning in HIV positive patients with HL, the same investigations and response criteria used in HIV-negative patients should be followed. Thus, assessment after treatment should include an FDG-PET scan and a BM biopsy if the BM was involved at diagnosis. These investigations should be performed at least 4–6 weeks after the last cycle of chemotherapy.

Regarding follow-up, several (empirically defined) schedules have been recommended for patients in CR, from 2–4 months for the first 2 years and from 3 to 6 months for the subsequent 3 years [34,67]. Investigations at follow-up should include medical history, physical examination and blood tests. No further surveillance investigations are recommended for patients in CR [68]. Patients who have received RT should have thyroid function tests checked regularly and female patients treated with Mantle RT should have surveillance mammography [34,67].

9.9.1 Recommendations

Assessment of response after treatment should be performed by FDG-PET scan and BM biopsy (level of evidence 1D).

Assessment during follow-up should be performed every 2–4 months during the first 2 years and every 3–6 for 3 further years (level of evidence 1D).

Table 9.4 Risk factors defining treatment groups

Treatment group	EORTC/GELA	GSHG
Limited stage ('Early')	CS I–II without risk factors (supra-diaphragmatic)	CS I–II without risk factors
Intermediate stage ('Early unfavourable')	CS I–II with ≥ 1 risk factors (supra-diaphragmatic)	CS I, CS IIA with ≥1 risk factors; CS IIB with risk factors C/D but no A/B
Advanced stage	CS III–IV	CS IIB with risk factors A/B; CS III–IV

Risk factors	EORTC/GELA	GSHG
	(A) large mediastinal mass	(A) large mediastinal mass
	(B) age ≥50 years	(B) extra-nodal disease
	(C) elevated ESR	(C) elevated ESR
	(D) ≥4 nodal areas	(D) ≥3 nodal areas

EORTC/GELA: European Organization for Research and Treatment of Cancer/Group d'Etude des Lymphomes de l'adult; GHSC: German Hodgkin Study Group.

Table 9.5 CR/CRu, EFS, DFS and OS in patients treated with ABVD according to their serological status [17]

End-point	HIV-negative (n=131)	HIV-positive (n=93)
CR/CRu	79%	74%
5-year EFS	66%	59%
5-year DFS	85%	87%
5-year OS	88%	81%

CR/CRu: complete response/complete response uncertain; EFS: event-free survival; DFS: disease-free survival; OS: overall survival.

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10.0 Multicentric Castleman's disease

10.1 Introduction

The first description of Castleman's disease appeared as a case record of the Massachusetts General Hospital in the New England Journal of Medicine in 1954 [1]. Benjamin Castleman, pathologist at Massachusetts General Hospital, subsequently described 13 cases of asymptomatic localized mediastinal masses demonstrating lymph node hyperplasia resembling thymoma in 1956 [2]. Multicentric Castleman's disease (MCD) is a relatively rare lymphoproliferative disorder that classically presents with fevers, anaemia and multifocal lymphadenopathy and, is now most commonly diagnosed in individuals infected with HIV type 1.

Castleman's disease is classified into localized (LCD) and multicentric (MCD) forms. The localized form usually presents in young adults with isolated masses in the mediastinum (60–75%) or neck (20%) or less commonly with intra-abdominal masses (10%). Systemic symptoms are rare with localized Castleman's disease. In contrast, MCD is associated with multi-organ systemic features, and follows a more aggressive course . Histologically, symptomatic MCD is predominantly due to the plasma cell variant (as opposed to the asymptomatic hyaline vascular variant) characterized by large plasmablasts in the mantle zone [3].

MCD occurs in the fourth or fifth decade of life in HIV-negative people but at younger ages in those who are HIV-positive. MCD has been also been reported with HIV-2 [4] and in a non-HIV-infected paediatric patient [5]. MCD presents with generalized malaise, night sweats, rigors, fever, anorexia and weight loss. On examination, patients have widespread lymphadenopathy, often accompanied by one or more of hepatosplenomegaly, ascites, oedema and pulmonary and pericardial effusions. Laboratory investigations may reveal thrombocytopenia, anaemia, hypoalbuminaemia and hypergammaglobulinaemia. Haemophagocytic lymphohistiocytosis may be also be present and confirmed by bone marrow examination [6]. Patients may also present with pancytopenia and renal respiratory failure (MCD is more likely to lead to neuropathic complications than locally confined Castleman's disease. Other less common complications include polyneuropathy and leptomeningeal and central nervous system (CNS) infiltration with central pontine myelinolysis [7] as well as myasthenia gravis [8]. The polyneuropathy is a chronic, inflammatory demyelinating neuropathy and may be present as part of the rare POEMS syndrome (Crow–Fukase disease)[9]. Primary effusion lymphoma (PEL), also driven by HHV8, can develop in the presence of MCD [10], demonstrating an association between these conditions although a definite clonal relationship has not been demonstrated. A study by Chadburn *et al*. [11] indicated that, although both PEL and MCD originate from HHV8-infected pre-terminally differentiated B cells, HIV-positive MCD arises from extrafollicular B cells, whereas PELs originate from cells that have traversed the germinal centre.

MCD is a relapsing and remitting disease and the definition of an 'attack' has recently been proposed as a combination of fever and a raised serum C-reactive protein plus three of the following symptoms: peripheral lymphadenopathy, splenomegaly, oedema, pleural effusion,

ascites, cough, nasal obstruction, xerostomia, rash, central neurological symptoms, jaundice or autoimmune haemolytic anaemia [12].

There is an association between MCD and AIDS-associated Kaposi's sarcoma (KS) [13]. In 1994, Chang and Moore isolated a new human gamma-2 herpesvirus from AIDS-KS lesions using differential representational analysis [14]. This virus, known as human herpesvirus 8 (HHV8) or Kaposi's sarcoma herpesvirus (KSHV), was later found to be present in all cases of HIV-associated MCD [15].

The role of combination antiretroviral therapy (cART) and CD4 level in preventing the emergence of MCD, in treatment or in preventing relapse remains unclear. Powles *et al*. [16]. showed that the risk of MCD was related to a nadir CD4 greater than 200 cells/mL, older age, no previous cART and a non-Caucasian background. In one small series 7/8 patients who were receiving cART at the time of presentation of MCD, had a median CD4 cell count of 385 (140–950) cells/mL [17]. Therefore MCD can present in the context of a well-preserved immune system.

Westrop *et al*. [18] suggested that the 2.4 higher incidence of MCD in patients of African ancestry presenting with HHV8-related malignancies might be due to the three-times higher frequency of the A299G single nucleotide polymorphism.

10.2 Diagnosis

The first step towards making the diagnosis of MCD in HIV infection is to consider it in those with suggestive symptoms, despite well-controlled HIV. CT scans of the neck, chest, abdomen and pelvis are useful to demonstrate lymphadenopathy, organomegaly and to direct tissue sampling [19]. The diagnosis of MCD can only be established definitively by lymph node biopsy. The characteristic features of HIV-associated MCD are a characteristic 'onion-skin' appearance and interfollicular plasmablasts that express the HHV8 latent nuclear antigen (LANA). These plasmablasts also express high levels of λ light-chain restricted immunoglobulin M (IgM), but are polyclonal and do not contain somatic mutations in their IgV genes, suggesting that they arise from naive B lymphocytes [20]. Occasionally these plasmablasts join together to form clusters or 'microlymphomas' and may progress to monoclonal plasmablastic lymphomas [3]. HHV8 is also present in the malignant cells of these plasmablastic lymphomas [21,22].

HHV8 encodes a viral homologue of interleukin-6 (vIL-6) as a lytic virokine. Only 10–15% of HHV8-positive plasmablasts in MCD express vIL6; however, the human IL-6 receptor is expressed by all HHV8-positive plasmablasts. It is hypothesized that activation of the IL-6 signalling pathway by HHV8 vIL-6 may transform naive B cells into plasmablasts and lead to the lymphoproliferative diseases associated with this virus, including MCD. Detection of HHV8 by PCR in lymph nodes may represent latent infection but may be absent in a minority (1/10) patients with MCD [23]. The presence of HHV8 IL-6 in lymph nodes of patients with MCD and no risk factors for HIV was associated with poor survival and lack of HHV8 IL-6, with low risk for subsequent lymphoma [24]. Bacon *et al*. [25] examined bone marrow aspirates and biopsies from 13 cases of MCD (11/13 HIV positive) and 66 control cases and suggested that the

presence of HHV8+ plasmablasts within lymphoid follicles and, or the interstitium of the bone marrow are helpful features for the early diagnosis of MCD.

Laboratory studies should include testing for HHV8 DNA in plasma or from peripheral blood mononuclear cells by real-time polymerase chain reaction (PCR). Preliminary studies suggest that plasma HHV8 viral load may be a usable tumour marker in HIV-associated MCD, helping in the diagnosis of MCD and in monitoring of responses to treatment and in the diagnosis of relapses [2,26]. Chilton *et al*. [27] demonstrated that HHV8 levels may become detectable up to 6 months before the onset of symptoms. Fish and Paul [28] showed that while HHV8 viral loads were significantly higher in MCD than KS, the usefulness of this observation was limited by some degree of overlap. A low HHV8 viral load (<2000 copies/ml) may be useful in excluding a diagnosis of MCD. Sayer *et al*. [29] reported that a cut-off of >1000 copies of HHV8/ml helped to discriminate between MCD and other diagnoses such as KS and lymphoma with a specificity of 94.7% and a negative predictive value of 97.3%. Polizzotto *et al.* [30] demonstrated that in 21 patients experiencing 34 flares of inflammatory symptoms e.g. fevers, elevated levels of HHV8 were associated with low haemoglobin, sodium and albumin and splenic enlargement. Stebbing *et al*. [31], showed that in 52 individuals with MCD, relapses were strongly associated with rising levels of HHV8 which predicted an attack (hazard ratio 2.9; 95% CI 1.3–6.7).

10.2.1 Recommendations

We suggest that histological confirmation requires immunocytochemical staining for HHV8 and IgM lambda (level of evidence 2B).

We suggest that all patients should have their blood levels of HHV8 measured to support the diagnosis (level of evidence 2C).

10.3 Staging

Following diagnosis, patients should have a CT of neck, chest, abdomen and pelvis. It is unclear whether a bone marrow biopsy to exclude microlymphoma should be required where HLH is suspected. The role of functional imaging such as fluorodeoxyglucose positron emission tomography (FDG-PET) scans is uncertain although a small study [32], indicated that in individuals with active MCD, FDG-PET scans more frequently detected abnormal uptake than CT

10.4 Prognosis

HIV-associated MCD is relatively uncommon and only recently recognized, so the incidence and prognosis are not well established. The precise effect of cART on incidence and prognosis is similarly unclear. Not only is MCD itself potentially fatal as a result of organ failure but it is also associated with an increased incidence of non-Hodgkin's lymphoma (NHL). In a prospective study of 60 HIV-infected individuals with MCD, 14 patients developed HHV8-associated NHL. Three patients had classic HHV8-positive, Epstein–Barr virus (EBV)-positive primary effusion lymphoma (PEL); five were diagnosed with HHV8-positive/EBV-negative visceral large B-cell lymphoma with PEL-like phenotype, and six developed plasmablastic lymphoma/leukaemia [22]. This is a 15-fold increase in lymphoma risk above that seen in the general HIV-infected population. In another study of 61 patients [33], at diagnosis, four patients (7%) had histological

evidence of coexisting lymphoma, one developed lymphoma 2 years after treatment. The incidence of lymphoma is 28 per 1,000 patient years. The pathogeneses of these lymphomas probably differ, with the plasmablastic type driven by the expansion of plasmablastic microlymphomas seen in MCD lesions [34,35]. In contrast, the PEL and PEL-like lymphomas may be driven by the cytokine-rich environment with high levels of IL-6 and IL-10, which are known to enhance cell growth of PEL cell lines [36].

Cattaneo *et al*. [37], in a retrospective study showed that cART did not improve the outcome in HIV-related MCD. Thirty-five patients over a 21-year period (9 pre-cART and 26 post-cART) were compared. Overall survival of the entire series was 28 months without significant differences between pre and post cART era. Causes of death were evaluable in 18: non-Hodgkin lymphoma (NHL) (7), MCD (6), opportunistic infections (1), liver cirrhosis (1), acute myocardial infarction (1), KS (1) and therapy-related toxicity (1). NHL and MCD were the most frequent cause of death in the post-cART era (4 and 5 of the 10 cases, respectively). The authors concluded that that the prognosis of HIV-related MCD remains poor even after the advent of cART. Unlike other lymphoproliferative disorders, cART did not impact on outcome of HIV-related MCD, suggesting that MCD can 'escape' immune reconstitution. A concomitant diagnosis of NHL and uncontrolled MCD seemed to be the main reason for an unfavourable outcome, particularly in the post-cART era. New therapeutic approaches, including rituximab, should therefore aim at avoiding NHL transformation and controlling 'MCD-related cytokine storm'.

10.4.1 Recommendations

The risk of lymphoma in patients diagnosed with MCD is high (level of evidence 2C).

cART does not prevent MCD (level of evidence 2D).

A rise in plasma HHV8 level can predict relapse (level of evidence 2D).

10.5 Management

There are no definitive gold-standard treatments for MCD. Apart from a randomized controlled trial of valganciclovir treatment for suppression of HHV8 replication [38], the best evidence is derived from single centre cohort studies. Follow up is generally short.

10.6 Combination antiretroviral therapy (cART)

The effect of cART, chiefly in combination with cytotoxic chemotherapy, has been described in seven patients with MCD and HIV infection [39]. Six patients responded to chemotherapy, and immune reconstitution was described in five patients. However, patients continued to require long-term maintenance chemotherapy to prevent recurrence. The median survival was 48 months, longer than in the pre-cART era. Therefore, the principle that HIV should be fully controlled during and after treatment for MCD should be adhered to in order to try to prevent relapse of MCD and other HIV-related conditions.

10.7 Rituximab

The use of an anti-CD20 monoclonal antibody, rituximab, routinely prescribed as therapy for B-cell lymphomas and autoimmune diseases, to target HHV8-infected plasmablasts in MCD is a novel and potentially beneficial approach to the treatment of this disease. It was initially the subject of several case reports. These patients were often pre-treated with chemotherapy and follow-up was brief; nine of 11 experienced a complete response [40–46].

The efficacy and safety of rituximab in 21 consecutive patients with plasmablastic MCD have been investigated [47]. These individuals received four infusions of rituximab 375 mg/m^2 at weekly intervals and, of 20 evaluable patients, all achieved clinical remission with biochemical and haematological normalization, and 70% achieved a radiological response. The overall survival and disease-free survival at 2 years were 95% and 79%, respectively, and in three patients who relapsed, retreatment with rituximab was successful [48]. These data corroborate the benefit seen in the aforementioned case reports and demonstrate that rituximab therapy results in an impressive clinical, biochemical and radiological sustained response in HIV-related MCD.

In a further study of 24 patients dependent on chemotherapy for a median time of 13 months, sustained remission was achieved in 70% with this regimen of rituximab and cessation of chemotherapy at day 60 (the primary endpoint) [12]. In each of these large series, one patient died soon after rituximab administration as a result of overwhelming disease, and the main adverse event seen in these patients was reactivation of KS, which is intriguing and may have been attributable to the rapid B-cell depletion that is observed during rituximab therapy, or an immune reconstitution inflammatory syndrome to hitherto latent antigens [49]. Bower *et al*. [50] demonstrated after successful rituximab therapy, a significant reduction from baseline of the CD19 B-cell count, and reductions in the levels of the inflammatory cytokines IL-5, IL-6 and IL-10.

In the largest study to date [33], Bower *et al*. identified 61 HIV-positive patients with histologically confirmed MCD (median follow-up, 4.2 years). Since 2003, 49 patients with newly diagnosed MCD have been treated with rituximab with (n = 14) or without (n = 35) etoposide. With rituximab-based treatment, the overall survival was 94% (95% CI, 87% to 100%) at 2 years and was 90% (95% CI, 81% to 100%) at 5 years compared with 42% (95% CI, 14% to 70%) and 33% (95% CI, 6% to 60%) in 12 patients treated before introduction of rituximab (log-rank P <0.001). Four of 49 rituximab-treated patients have died; three died as a result of MCD within 10 days of diagnosis, and one died as a result of lymphoma in remission of MCD. Eight of 46 patients who achieved clinical remission suffered symptomatic, histologically confirmed MCD relapse. The median time to relapse was 2 years, and all have been successfully re-treated and are alive in remission. The 2- and 5-year progression-free survival rates for all 49 patients treated with rituximab-based therapy were 85% (95% CI, 74% to 95%) and 61% (95% CI, 40% to 82%), respectively.

Gerard *et al.* [51] compared the incidence of NHL between patients who had received rituximab or not over 4.2 years of follow up. In the group that did not receive rituximab (n = 65), 17 patients developed patient developed NHL (incidence, 4.2 of 1000 person years). Based on the

propensity score-matching method, a significant decrease in the incidence of NHL was observed in patients who had been treated with rituximab (hazard ratio, 0.09; 95% confidence interval, 0.01–0.70). Ten Kaposi sarcoma (KS) exacerbations and one newly diagnosed KS were observed in nine patients after rituximab therapy. Rituximab was associated with an 11-fold lower risk of developing lymphoma. KS exacerbation was the most challenging adverse event after rituximab therapy.

Data from Stebbing *et al*. [31] showing that rising levels of HHV8 predicted relapses, suggested that combination therapy including rituximab should be considered.

10.8 Chemotherapy

For immunocompetent patients the chemotherapy regimens for MCD are based on lymphoma schedules such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) [52]. Although there is little evidence on which to base treatment strategies in HIV-associated MCD, many centres use single-agent chemotherapy with vinblastine or etoposide to induce remission in aggressive forms of MCD. This may be followed by maintenance [53].

10.9 Immunotherapy (excluding rituximab)

Specific immunotherapy has also been used as treatment for MCD. Interferon alpha (IFN-α) has been administered either alone or in combination with cART or chemotherapy for patients with MCD both to induce remission and as maintenance therapy [52,54,55]. IFN-α used in combination with vinblastine and splenectomy, contributed to the long-term remission of two of three patients [52]. In a case report a patient was initially treated with antiviral therapy and splenectomy followed by chemotherapy to induce remission and, after relapse IFN-α therapy [55] led to remission for over a year. A further case report of treatment of MCD with cART and low-dose IFN-α alone has shown a sustained remission of 24 months [56]. The case for steroid treatment, other than as an adjunct for chemotherapy regimens is unproven, although many practitioners advocate their use to prevent or lessen the effects of a cytokine ‘storm’.

As the pathogenesis of MCD is related to HHV8 virus and its viral oncogenes, particularly vIL-6, monoclonal anti-IL-6 therapy has also been used in the treatment of MCD. Seven HIV-negative patients were treated with atlizumab, a humanized monoclonal anti-IL-6 receptor antibody in patients with either multicentric plasma cell or mixed variant Castleman’s disease. They had resolution of their immediate symptoms and, by 3 months, all had reduction in lymphadenopathy and hypergammaglobulinaemia with improvement of renal function, the result of secondary amyloidosis. This remission was not sustained [57]. These studies have been expanded to a multicentre clinical trial in Japan [58] but there are no reports of the use of atlizumab in persons with HIV. In an ongoing phase I study, neutralization of IL-6 activity by Siltuximab has led to a high objective tumour response rate (52%) and clinical benefit rate (78%) in subjects with MCD with a favourable safety profile1. These results have prompted a trial to definitely assess the efficacy and safety of Siltuximab in combination with best supportive care (BSC) versus placebo + BSC which has not yet been published [59].

Recent case reports of treatment with thalidomide also showed resolution of systemic manifestations of MCD, and the patients included one with HIV [60,61]. Thalidomide is known to have a powerful anticytokine effect and inhibits tumour necrosis factor and other pro-inflammatory cytokines.

10.10 Anti-human herpes virus-8 therapy

As MCD has been shown to be a viral-driven disease, with the presence of viral genes such as vIL-6 having an effect on pathogenesis, the effect of anti-herpesvirus therapy to reduce the KSHV viral load and alleviate disease has been examined in HHV8-associated diseases in the HIV setting. In HIV-positive patients, KS incidence was reduced when prophylactic ganciclovir or foscarnet were used to prevent cytomegalovirus (CMV) retinitis [62,63]. Furthermore, antiviral treatment, which has led to a clinical improvement, has been shown to reduce HHV8 viral load in patients with KS [64], PEL and haemophagocytic syndrome [65]. In a series of three patients treated with ganciclovir, there was a reduction in the frequency of acute symptoms of MCD for two patients treated with oral and intravenous ganciclovir [66]. For the third patient, there was resolution of pulmonary and renal failure with intravenous ganciclovir. All the patients had a reduction in HHV8 viral load with the ganciclovir therapy, accompanying the resolution of their symptoms. However, the use of foscarnet and cidofovir antiviral therapy was ineffective in an HIV-negative MCD patient with proven HHV8 viraemia and treatment with corticosteroids in combination with chlorambucil chemotherapy was required to achieve a clinical response [67]. Furthermore, the HHV8 viral load rose in this patient with the commencement of anti-herpesvirus therapy; this may indicate that the antiviral therapy was ineffective in this case, or that, once the MCD is established, HHV8 has a less prominent role and antiviral therapy is less effective than immunotherapy or chemotherapy.

Caspar *et al*. [38] randomized 26 men with HHV8 infection to receive 8 weeks of valganciclovir administered orally (900 mg once per day) or 8 weeks of placebo. After a 2-week washout period, participants in each group received the study drug they had not yet taken (either valganciclovir or placebo), for 8 additional weeks. Oral swab samples were collected daily during the study, and HHV-8 and CMV DNA were quantified by real-time PCR. A total of 16 HIV-positive men and 10 HIV-negative men enrolled in, and completed the study. Of the 3439 swab samples that participants had been expected to provide, 3029 (88%) were available for analysis. HHV-8 was detected on 44% of swabs collected from participants who were receiving placebo, compared with 23% of swabs collected from participants who were receiving valganciclovir (relative risk [RR], 0.54, 95% CI, 0.33–0.90]; $P = 0.02$). Valganciclovir reduced oropharyngeal shedding of cytomegalovirus by 80% (RR, 0.20, 95% CI, 0.08–0.48; $P < 0.001$). Shedding of HHV-8 and shedding of cytomegalovirus were independent. Haematological, renal, or hepatic toxicities were no more common among participants who received the active drug, compared with those who received placebo, though participants who received valganciclovir reported more days of diarrhoea. Valganciclovir administered orally once per day is well tolerated and significantly reduces the frequency and quantity of HHV-8 replication.

A further study [68] compared the efficacy of valaciclovir, famciclovir and cART in reducing HHV8 oropharyngeal shedding in 6036 swabs from 58 participants. After adjusting for baseline

HIV viral load and cART use, an 18% reduction in HHV-8 shedding frequency was found in participants on valaciclovir and a 30% reduction on famciclovir. cART use was associated with an 89% reduction in HHV-8-shedding. Neither antiviral nor antiretroviral therapy was associated with decreased HHV-8 quantity. Valaciclovir and famciclovir were associated with modest but significant reductions in HHV-8 oropharyngeal shedding frequency. In contrast, HAART was a potent inhibitor of HHV-8 replication.

A novel therapeutic approach using zidovudine and valganciclovir to affect cells within which HHV8 lytic replication is occurring by targeting the HHV8 lytic genes ORF36 and ORF 21, which phosphorylate these drugs to toxic moieties was reported by Uldrick *et al*. [69] in 14 HIV positive patients with symptomatic HHV8-MCD. A total of 86% of patients attained major clinical responses and 50% attained major biochemical responses. Median progression-free survival was 6 months. With 43 months of median follow-up, overall survival was 86% at 12 months and beyond. At the time of best response, the patients showed significant improvements in C-reactive protein, albumin, platelets, human IL-6, IL-10, and KSHV viral load. The most common toxicities were haematological.

10.11 Surgery

Although surgery is the mainstay of treatment for LCD [70] with complete removal of the mediastinal lesions often curative, this has a limited role in MCD. Splenectomy, in addition to establishing the histological diagnosis, may have a therapeutic benefit as a debulking procedure, as some of the haematological sequelae such as thrombocytopenia and anaemia may in part be caused by splenomegaly. Following splenectomy there is often resolution of the constitutional symptoms but this may be short-lived, approximately 1–3 months, and some form of maintenance therapy is needed to prevent relapse [52].

10.12 Recommendations

We suggest that histological confirmation requires immunocytochemical staining for HHV8 and IgM lambda (level of evidence 2B).

We suggest that all patients should have their blood levels of HHV8 measured to support the diagnosis (level of evidence 2C).

We suggest that the risk of lymphoma in patients diagnosed with MCD is high (level of evidence 2C).

We suggest that cART does not prevent MCD (level of evidence 2D).

We suggest that a rise in plasma HHV8 level can predict relapse (level of evidence 2D).

We recommend that rituximab should be first line treatment for MCD (level of evidence 1B).

We recommend that chemotherapy should be added to rituximab for patients with aggressive disease (level of evidence 1C).

We recommend re-treatment with rituximab based therapy for relapsed MCD (level of evidence 1C).

We suggest clinical monitoring for patients in remission should include measurement of blood HHV8 levels (level of evidence 2C).

10.13 Auditable outcomes

Proportion of patients with MCD treated with rituximab as first-line treatment.

Proportion of patients with aggressive MCD treated with rituximab and chemotherapy.

Proportion of patients with relapsed MCD re-treated with rituximab.

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11.0 Non-AIDS-defining malignancies

11.1 Introduction

This section aims to address the evidence-based guidelines for non-AIDS-defining cancers in people with HIV infection. It will exclude Hodgkin's disease and anal cancer, which have been covered already. The cancers it will specifically address are:

- Testicular germ cell tumours
- Non-small cell lung cancer (NSCLC)
- Hepatocellular cancer (HCC)

There is very limited data available on:

- Colon cancer
- Head and neck cancer
- Melanoma
- Other urological cancers
- Haematological cancers
- Breast cancer

Therefore, these patients should be managed by oncologists and HIV doctors together, according to standard guidelines for HIV-negative patients. We suggest that careful attention to the drug interactions between cytotoxic chemotherapy and antiretroviral agents is needed, as well as focus on opportunistic infection prophylaxis.

11.2 Testicular germ cell cancers

11.2.1 Introduction

It appears that only seminoma (as opposed to non-seminoma germ cell tumours) occurs more frequently in HIV infection [1]. There is no clear consensus on the exact relative risk but it ranges between approximately 3 and 7 [1-5]. There is no evidence that the incidence is increasing in the era of HAART [1]. The cause for this increased incidence is unclear although chronic immune suppression has been suggested. Patients present with only moderate immune suppression and they appear to be about 10 years younger than their HIV-negative counterparts [1]. There is conflicting evidence that patients present with more advanced disease. This may be because of the increased incidence of para-aortic lymphadenopathy in HIV disease incorrectly up-staging patients from stage I to stage II disease [6]. Patients with HIV-related testicular cancer have a similar cancer-free outcome compared to their HIV-negative counterparts if treated in an identical manner in the HAART era [1]. This contradicts early reports in the pre HAART era [7].

11.2.2 Diagnosis, staging, prognostic factors

Diagnosis should follow an identical path regardless of HIV status and all patients should be tested for HIV infection. A testicular mass must be treated with the utmost suspicion and an ultrasound scan (or MRI) and tumour markers (AFP, HCG) should follow. LDH is non-specific and should only be used to prognosticate patients with metastatic disease. False positive AFP can be related to HAART/hepatitis-related liver disease, while there are many causes of a false positive LDH [1].

The differential diagnosis for a testicular mass in this setting includes orchitis and lymphoma. A CT scan of the chest abdomen and pelvis should be performed for full staging. MRI scanning for para-aortic lymph nodes is an alternative for the abdomen and pelvis. There is no clear role for FDG-PET in these patients regardless of HIV serostatus.

11.2.3 MANAGEMENT

11.2.3.1 Stage I disease

Patients with stage I disease (seminomas or NSGCT) can be safely treated with surveillance alone and have a similar outcome to their HIV-negative counterparts [1]. Alternatively, adjuvant carboplatin (AUC7) can be offered to the seminoma patients (we advise one cycle), while two cycles of adjuvant BEP can be offered to the NSGCT [1]. It appears three cycles of BEP suppresses the CD4 cell count by between 25 and 50%, and it is probable that two cycles of BEP will also be suppressive. Therefore low-risk NSGCT patients should be offered surveillance and adjuvant therapy should only be considered for high-risk NSGCT [6]. Additionally it has been suggested that adjuvant therapy should be considered in patients with either a haphazard life style (who are unlikely to co-operate with an intensive surveillance programme) [6]. Patients should receive HAART during adjuvant or metastatic chemotherapy [1]. Prophylactic antifungal agents should be considered, especially for patients receiving two cycles of BEP [6].

11.2.3.2 Metastatic disease

Patients should be risk stratified according to the IGCCCG guidelines in an identical manner to HIV-negatives [8]. Good-risk patients should be offered three cycles of standard 5-day BEP with concurrent HAART and prophylactic anti-fungals should be considered [1,6]. One should expect a 50% drop in the CD4 cell count with chemotherapy [6,9]. Treatment modifications should follow the HIV-negative model. Those with extensive pulmonary limitation from previous infection can alternatively have four cycles of EP chemotherapy [8]. Carboplatin should not be used as a substitute for cisplatin and dose modifications/delays should be avoided where possible. Growth factors such as GCSF should be considered where appropriate [8].

Patients with intermediate- and poor-risk disease should be offered four cycles of standard 5-day BEP chemotherapy [1,6]. Those with extensive pulmonary limitation from previous infection can alternatively have four cycles of VIP chemotherapy. The two regimens have a similar outcome in HIV-negatives but VIP is more myelosuppressive in HIV-negatives [8]. Other regimens for poor-risk patients (such as high-dose therapy and dose-dense therapy) have not been shown to be superior to four cycles of BEP in HIV-negatives. Patients should receive concurrent HAART and chemotherapy antifungal prophylaxis should be considered where appropriate.

11.2.3.3 Relapsed disease

There is very limited data on the treatment of relapsed disease [1]. Patients should be treated in an identical manner to HIV-negatives. The TIP regimen seems appropriate for patients who relapsed 6 months after initial diagnosis [8]. High-dose chemotherapy followed by autologous peripheral blood stem-cell transplant is generally considered the only curative option after two or more treatment regimens in HIV-negative patients, and although data is limited in HIV-positive patients this treatment should be considered for early relapse [10]. Third-line therapy is usually palliative and there is no data regarding this in men living with HIV/AIDS. It is clear that single-agent therapy has little activity in this setting in HIV-negatives.

11.2.4 Summary

Seminoma of the testis is more common in men living with HIV infection.

Germ cell tumours of the testis should be treated in an identical manner regardless of HIV status (level of evidence 2C).

Men living with HIV who require chemotherapy for germ cell tumours should receive concomitant HAART and opportunistic infection prophylaxis (level of evidence 2C).

Surveillance for stage I disease is safe (level of evidence 2C).

Bleomycin can be avoided if necessary in the management of these patients (level of evidence 2D).

11.3 Non-small cell lung cancer

11.3.1 Introduction

It appears that the incidence of non-small cell lung cancer (NSCLC) is increased in people living with HIV infection [11,12]. Not all of this increase in incidence can be attributed to smoking cigarettes [12] although cessation of smoking should be recommended for people living with HIV/AIDS. There is no evidence of an increased incidence of small cell lung cancer (SCLC) in HIV and no specific data on this issue [11,12]. It is recommended that patients with SCLC are treated in an identical manner to their HIV-negative counterparts. What anecdotal data are available suggest these patients do badly.

Patients with HIV-related NSCLC present at a younger age and with more advanced disease than their HIV-negative counterparts [11-13]. The rise in incidence of adenocarcinoma in the HIV-negative population has also been seen in people living with HIV/AIDS [14].

11.3.2 Prognosis

Studies in the pre-HAART era showed HIV-positive NSCLC patients have a significantly worse outcome compared to their HIV-negative counterparts. These studies were small and were not all age- or stage-matched, however, the results were compelling with a median survival of only 3 months [15,16]. Although initial reports did not suggest that HAART had a huge impact, with average survival still only 4 months, later studies have found a median survival of up to 9 months in advanced stage disease although this is still less than that reported in clinical trials from the general population [13,17]. This poorer outcome may just reflect more advanced disease and, when this taken in account, the true prognosis may well be

similar in HIV-positive and -negative populations [13]. It is clear that there is a delay in the diagnosis of HIV-positive lung cancer patients and this may in part be due to the wide differential diagnosis of an HIV patient with a mass in the lungs [14].

11.3.3 Management

As HIV patients with NSCLC present at a younger age than HIV-negatives, a mass on chest X-ray should raise the suspicion of NSCLC. It is recommend that in addition to a tissue diagnosis, patients should have a CT of the chest and abdomen (including adrenals), and bone scan. If an individual is still potentially operable then a mediastinoscopy should be performed. In view of the possible decreased specificity and lack of data regarding FDG-PET in HIV-positive lung cancer, PET results should be interpreted with caution. Patients should not necessarily be deemed inoperable on the evidence of FDG-PET alone. The results of FDG-PET should be considered in conjunction with HIV status (HIV history, opportunistic infections, viral load and CD4 cell counts). Cranial imaging is indicated in patients eligible for loco-regional treatment, or in the presence of clinical symptoms.

11.3.3.1 Operable disease

Those with operative disease should be offered curative surgery, once staging investigations are complete; however, studies suggest that a small minority of HIV-positive lung cancer patients are actually offered this [14]. This is due to a combination of patients presenting with advanced disease and co-morbidity. Although 30-day post-operative mortality is comparable to that in the general population, there is an increase in complications and recurrence, whilst overall survival is reduced [18]. The latter are most pronounced if the CD4 cell count is below 200cells/µL, and so should be considered.

There is no data regarding the use of adjuvant chemotherapy in HIV-related lung cancer, therefore these patients should follow the HIV-negative lung cancer guidelines. Chemotherapy should consist of standard regimens and doses. HAART should continue throughout treatment. Follow-up should be as with HIV-negative patients.

11.3.3.2 Locally advanced disease

There is no data specifically addressing this issue. Patients with locally-advanced disease should be offered chemo-radiation according to HIV-negative guidelines. It is noteworthy that grade 3/4 treatment–associated toxicities have been reported in 60% of HIV positive lung cancer patients, whilst chemoradiotherapy is associated with profound immunosuppression in other HIV-positive tumours [19,20]. Patients should therefore continue/commence HAART and antifungal prophylaxis where appropriate.

11.3.3.3 Metastatic disease

The presence of activating mutations within the epidermal growth factor receptor (EGFR) gene of lung cancer cells makes these tumours highly sensitive to EGFR-targeting tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib [21,22]. The incidence of such mutations in HIV-associated lung cancer is not known; however, individual cases treated with EGFR TKIs have been reported, demonstrating the feasibility of this approach [23]. Consequently all patients with advanced stage NSCLC should be screened for EGFR mutations as in the general population. Use of EGFR TKIs requires caution due to potential interaction with HAART through induction of cytochrome P450 isoenzyme CYP3A4. Data from KS suggests that TKIs do indeed potentiate the side effects of HAART [24].

In the absence of an activating EGFR mutation, standard chemotherapy regimens are indicated in the first-line setting. Experience shows that treatment tends to be tolerated poorly and response rates are low (<30%), with deaths attributable to cancer and not opportunistic infections [17]. There are currently no data on second- and third-line chemotherapy for metastatic NSCLC. Management should follow therefore HIV-negative guidelines.

11.3.4 HAART

Good control of HIV infection is important because median survival is improved if the CD4 cell count is >200 cells/µL [20,25,26]. However concurrent use of HAART and chemotherapy can be problematic, with a significant increase in myelosuppression reported for patients also taking protease inhibitors [26]. As such, it may be worth interrupting HAART prior to chemotherapy if the patient's HIV is well controlled [14,17].

11.3.5 Screening

CT screening for lung cancer in the HIV-negative population is associated with a 20% decrease in lung cancer mortality. Although large-scale data from the HIV-positive population is lacking, CT screening in this patient group is feasible, whilst concerns about poor specificity may be unfounded [27,28]. However, in the absence of a national programme, screening is not recommended with either CXR or CT.

11.3.6 Summary

HIV-positive patients should be encouraged to stop smoking cigarettes (level of evidence tbc).

Patients should be offered potentially curative surgery where appropriate (level of evidence 2C).

Patients should be screened for activating EGFR mutations and treated with EGFR TKIs by a team experienced in the use of HAART (level of evidence 2D).

There is currently no role for screening for lung cancer in people living with HIV (GPP).

11.4 Hepatocellular cancer

11.4.1 Introduction

There is debate as to whether there is an increased incidence of HCC in HIV-positive individuals. This uncertainty is primarily because HBV and HCV act as confounding factors in this setting. In view of the long delay between development of cirrhosis and subsequent HCC in both HIV-positive and HIV-negative populations an increase in the incidence of this disease in HIV may have not occurred yet [29].

In Western countries approximately 30% of people with HIV are co-infected with HCV, rising to approximately 75% in IV drug users [30]. HIV affects the natural history of HCV infection in two important ways: first, it increases the likelihood of chronic infection following the acute episode and secondly, it hastens the development of cirrhosis once chronic infection is established. This has important implications for the subsequent development of HCC and screening strategy [29].

HBV is directly carcinogenic and may promote the development of HCC in the absence of cirrhosis, especially in populations where HBV may have been acquired at birth and in early childhood [31]. It has also become evident that high HBV viral loads may be linked to the development of HCC [32]. It is probable that a lower CD4 cell count, particularly in the context of HBV co-infection, is associated with a higher risk of HCC [33].

HIV co-infection also accelerates the progression of HBV infection [34]. There is a large regional variation in the proportion of people with HIV who have previously been exposed to HBV (10–90%). Retrospective series suggest that HBV is responsible for a much smaller proportion of HCC compared to HCV in HIV-positive individuals [29,30].

11.4.2 Presentation and diagnosis

HIV-positive HCC patients are younger and are more often HCV positive [30,35-37]. The majority of the HIV cohort has HCV and cirrhosis. The great majority of HIV-positive HCC patients are on HAART at diagnosis and consequently they tend to be only moderately immunosuppressed [30,35]. There appears to be no significant difference between HIV-positive and -negative patients in the Barcelona Clinic Liver Cancer (BCLC) stage at presentation [35].

Most HCCs are identified with US scanning and AFP levels [30]. The degree of cirrhosis should be assessed prior to any definitive treatment using the Child–Pugh classification. HIV-positive HCC patients are more likely to have compensated liver disease (Child–Pugh A). A CT scan of the chest, abdomen and pelvis is required to exclude metastatic disease.

11.4.3 Management

Initial series in HIV-positive individuals with HCC showed that the majority of patients were not being offered active treatment and that consequently outcome was poor [30]. Although more recent work has shown an improvement in the situation [35], others report that one third of patients remain untreated and even in those with potentially curable disease, one-quarter receive less effective treatment than is indicated [38].When HIV patients are offered active treatment they have a similar survival to their HIV-negative counterparts [35,37,39-41].

Whether HIV status is itself related to survival remains uncertain. One series comparing 65 HIV-positive and 267 HIV-negative patients with HCC found that HIV status negatively influenced outcome in both treated and untreated patients [42], whilst HIV-associated HCC patients have a higher drop-out rate pre-transplantation and appear to have a more aggressive overall disease course [36]. In contrast others report no difference in survival with respect to HIV status, and that prognosis is instead governed by liver function, tumour bulk and cancer treatment [35].

Control of HIV infection in HCC is important. Patients with a CD4 cell count >200 cells/μL have lower AFP levels, are more likely to receive active treatment, and have a better median survival (11.7 months vs. 5.2 months) [43]. Correspondingly, an undetectable HIV RNA viral load (<400 copies/ml) is associated with a lower Child–Pugh score and a better median overall survival. The latter is only seen in untreated patients [44]. The degree of immunosuppression does not appear to correlate with BCLC stage [43,44]. Since use of HAART correlates with better overall survival, it is recommended for HIV-positive HCC patients [42].

11.4.3.1 Localised therapies

In the HIV-negative population, solitary or a small number of HCC lesions are resectable. If complete resection is possible this should be performed without biopsy. These patients should have category A cirrhosis according to Child–Pugh classification [45]. This approach is associated with a 5-year survival of 60–70% in the HIV-negative population [46] and so HIV-positive patients should be considered for such treatments. Other options for patients with localised disease in whom resection is not possible include ethanol injection, radiofrequency ablation or trans-arterial chemo-embolization.

11.4.3.2 Transplantation

It appears that transplantation may have superior results to resection alone in HIV-negative patients [47]. According to the Milan criteria, transplantation should be considered if there are three liver lesions less than 3 cm or one lesion less than 5 cm in diameter. Several series have reported on liver transplantation for HIV-associated HCC. Eligible patients tend to be younger and, although there is a higher drop-out rate compared to HIV-negative patients, there is no significant difference in overall survival or relapse between the two groups [48]. 3-year overall survival of 74% and 3-year relapse free survival of 69% are reported [48]. Consequently HIV-positive patients should be considered for transplantation in the same way as HIV-negative patients. HIV status itself is not a prognostic factor for HCC patients undergoing liver transplantation [48].

Special attention is required for HIV-positive liver transplants due to the potential interaction between HAART and immunosuppressive therapy such as tacrolimus. This is particularly true for inhibitors of cytochrome P450 such as protease inhibitors.

11.4.3.3 Sorafenib

Sorafenib, an oral multi-TKI targeting the Raf cascade as well as vascular endothelial growth factor/platelet-derived growth factor receptors on tumour cells, significantly prolongs survival in HIV-negative patients with advanced, treatment-naïve HCC [49]. Early case studies reports of sorafenib in HIV-positive HCC suggested synergy with HAART, with impressive response rates but more marked toxicity [50]. The largest series of HIV-positive HCC treated with sorafenib involves 27 patients and reported partial response in 11% and stable disease in 44% [51]. In contrast to the earlier case studies, there were no reports of complete responses. Median time to progression was 5.1 months and median overall survival was 12.8 months from start of sorafenib. Toxicities, principally diarrhoea and hand-foot syndrome, were more severe than expected suggesting possible interaction with concomitant use of HAART [51]. Pharmacokinetic studies are of HAART and sorafenib are ongoing.

11.4.4 Screening for HCC in patients with hepatitis and HIV co-infection

Recommendations for screening for patients with hepatitis and HIV co-infection exist in BHIVA as well as European Association for Study of the Liver (EASL)-American Association for the Study of Liver Disease (AASLD) guidelines [52]. Screening programmes utilizing serum AFP and 6-monthly ultrasound scans (USSs) have demonstrated improved survival in non-HIV-infected patients [57]. Although AFP may not add to the value of USSs if the latter is done twice or more a year, this frequency of scans is often impractical and therefore AFP is still used. HBV is potentially oncogenic, and so even in the absence of cirrhosis it is advised

that all HIV/HBV co-infected patients have 6-monthly US scans even in the absence of cirrhosis.

Adherence to published guidelines is poor, and many at-risk cohorts do not receive adequate USS screening [53]. Surveillance for HCC needs to be tailored to specific risk [54]. Some patients may warrant more intensive surveillance with shorter frequency [55] or difference imaging modalities as USS is associated with an appreciable false-negative rate [56].

11.4.5 Summary

We suggest that people living with HIV with HCC should be treated in a similar manner to their HIV-negative counterparts (level of evidence 2C).

We suggest that liver transplantation should be considered for appropriate cases, as in the HIV-negative population (level of evidence 2D).

We suggest that sorafenib is a treatment option in advanced, non-operable HCC (level of evidence 2D).

Noncirrhotic HBV coinfected patients should be considered for HCC screening (level of evidence tbc).

HCC screening with 6-monthly AFP and liver USS should be offered to all cirrhotic patients with HBV and HCV co-infections (level of evidence tbc).

11.5 Other cancers

11.5.1 Colorectal cancer

The largest prospective study to date compared 136 asymptomatic HIV-positive patients to 272 HIV-negative patients and found an increased incidence of neoplastic lesions (adenomas, adenocarcinomas) in the former [57]. HIV-positive patients with colorectal adenocarcinoma were significantly younger, had more advanced disease and had an increased prevalence of right-sided tumours [57], all of which is in keeping with findings from smaller studies [58-60]. Evidence for the treatment of HIV-positive colorectal cancer (CRC) patients is limited to small retrospective case studies and so specific recommendations are not possible. However it appears that standard chemotherapy in combination with HAART for patients with metastatic disease is feasible with no apparent increase in toxicity, no opportunistic infections during or after treatment, and an overall response rate of 50% [61]. Treatment of CRC reduces cellular immunity so use of HAART and prophylaxis against opportunistic infection is recommended [62].

Although some studies have found a poorer survival in HIV-positive CRC patients, others report no difference compared to matched HIV-negative controls [58,60]. Larger prospective studies investigating all disease stages are required. The increased incidence of colorectal cancer in HIV-positive patients suggests a role for screening in this patient group although no particular programmes can be recommended [57].

11.5.2 Others

Only case reports and small retrospective series exist for other malignancies. HIV-positive acute myeloid leukaemia patients achieve remission with intensive treatment but this is

poorly tolerated and most succumb to non-opportunistic infections. Survival is generally worse and CD4 cell count is a strong predictor of poor prognosis [63]. Head and neck cancers and breast cancers may be more aggressive than in their HIV-negative counterparts, although radiation therapy in the former appears to be well tolerated with expected toxicity profiles [64,65].

There is the decreased incidence of prostate and breast cancer in HIV, the reason for which does not appear to be related to hormone deficiency [2,66]. The reduced incidence of prostate cancer may be explained by differential PSA screening in the HIV-positive and general populations [67]. Small case studies suggest that HIV-positive patients with prostate cancer should be managed similar to their HIV-negative counterparts and that outcomes are not significantly altered by HIV status [68,69].

We recommend that patients with these less well-described cancers are offered the standard care offered to HIV-negatives. Treatment should be given in conjunction with HIV doctors. Prospective databases are required for this group.

11.5.3 Summary

We recommend that the management of people living with HIV with non-AIDS-defining malignancy should be in a centre with adequate experience and requires a joint MDT including both oncologists with experience of managing HIV-related malignancy and HIV physicians (level of evidence 1C).

We recommend that patients with NADM should be offered the standard care given to HIV-negative patients (level of evidence 1C).

We recommend that all potential interactions between HAART, opportunistic infection prophylaxis and cancer therapy should be considered (level of evidence 1C).

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12.0 Opportunistic infection prophylaxis in HIV associated malignancy

12.1 Introduction

HIV infection causes immunosuppression, CD4 lymphocyte count loss and a progressive risk of opportunistic infection and tumours. Similarly chemotherapy and radiotherapy for HIV-related malignancies is associated with an increased risk of infection secondary to the myelosuppression and additional CD4 lymphocyte count loss [1-3]. The risk of infection is further raised by the presence of central venous catheters [4-7], neutropenia associated with HIV infection [8,9] and many of the therapies utilized to treat HIV and its complications [10-12].These factors all combine to produce a significant risk of opportunistic infection in people living with HIV undergoing treatment for cancer.

Guidelines for the initiation of opportunistic infection prophylaxis and highly active antiretroviral therapy (HAART) are available [13] but these treatments should be started at higher CD4 cell counts in patients who are to undergo chemotherapy and radiotherapy. We recommend that all patients with AIDS-defining malignancies should start HAART (level of evidence 1B) [13]. We suggest that all patients with non-AIDS defining malignancies who are due to start chemotherapy or radiotherapy should be started on HAART unless contra-indicated (level of evidence 2C) [13]. This is based on the well-documented decline in CD4 cell counts associated with chemotherapy and radiotherapy. Although guidelines suggest initiation of prophylaxis against opportunistic infections based on CD4 cell count, this differs in those with malignancies due to the possible profound immunosuppression associated with chemotherapy and radiotherapy.

12.2 PCP prophylaxis

Prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) is recommended for those who have a CD4 count less than 200 cells/µL (level of evidence 1A) and should be considered at higher levels in all patients starting chemotherapy or radiotherapy (GPP) [14]. Chemotherapy and radiotherapy are associated with profound falls in CD4 cell counts even in patients on HAART and the degree of decline in CD4 cell count may be unpredictable [1-3]. The treatment of choice is co-trimoxazole, which may have additional benefits in reducing the incidence of bacterial infections (respiratory, gastrointestinal especially salmonella and possibly CNS infections) [15-18] and toxoplasmosis [19,20]. Alternative prophylaxis should be with dapsone or pentamidine via nebuliser.

12.3 MAC prophylaxis

Prophylaxis against MAC is recommended for individuals with a CD4 count less than 50 cells/µL (level of evidence 1B) [14]. Individuals who have or are at risk of a CD4 cell count falling below this level should be considered for MAC prophylaxis. The treatment of choice is azithromycin 1.25g once per week or clarithromycin with rifabutin being considered as an alternative [21-24].

12.4 Fungal prophylaxis

People living with HIV who have low CD4 cell counts are at risk of fungal infections, most commonly oral and oesophageal candida and cryptococcosis; whilst those with prolonged very low CD4 cell counts are also at risk of pulmonary aspergillosis. In individuals with central venous catheters *in situ* and profound neutropenia, invasive fungal infections are a considerable cause of morbidity and mortality.

A systematic review and meta-analysis of 31 trials of antifungal prophylaxis in cancer patients after chemotherapy or haematopoietic stem-cell transplantation (HSCT), showed that antifungal prophylaxis significantly decreases all-cause mortality (RR 0.84; 95%CI 0.84–0.95) and the effect estimates were greater in studies with more rigorous methodology [25]. Antifungal prophylaxis was also found to be of benefit in the secondary outcomes including risk of fungal-related death (RR 0.55; 95% CI 0.41–0.74), documented invasive fungal infection (IFI) (RR 0.5; 95% CI 0.41–0.61), any (documented, probable and possible) IFI (RR 0.64; 95% CI 0.56–0.73), and the use of empiric antifungal therapy (RR 0.83; 95% CI 0.78–0.88) [25].

Within the meta-analysis, seven trials [26-32] compared fluconazole with itraconazole; overall there was no significant difference in all cause mortality, fungal-related mortality, documented IFI, or invasive *Candida* or *Aspergillus* infections [25]. Itraconazole use, however, was associated with significantly more adverse events causing discontinuation of the drug. Itraconazole also interacts with vinca alkaloids so should be avoided in regimens containing vincristine, vinblastine, vindesine or vinorelbine [33].

Two trials have compared posaconazole to oral fluconazole or itraconazole [34,35]. Posaconazole use resulted in a reduction of all cause mortality of borderline significance (RR 0.77; 95%CI 0.59–1.01). There was a significant reduction in fungal-related mortality (RR 0.25; 95% CI 0.11–0.57) and documented invasive *Aspergillus* infections (RR 0.22; 95% CI 0.11–0.42) but no difference in adverse reactions leading to discontinuation of the antifungal drug [25]. Posaconazole also has adverse interactions with vinca alkaloid chemotherapy [33].

The efficacy of voriconazole compared with fluconazole was examined in a large (*n*=600) randomized double-blind trial of allogenic HSCT recipients [36]. No difference in fungal free-survival was found but there was a trend towards lower incidence of *Aspergillus* infections, incidence of IFI, and less use of empiric antifungal therapy. Voriconazole use however may be associated with severe photosensitivity and other adverse events [37-39] and also has adverse interactions with vinca alkaloid chemotherapy [33].

Although the evidence for systemic azole antifungal prophylaxis comes from haematological malignancy in the HIV seronegative or untested population, there is an added risk of invasive fungal infection in people living with HIV. We recommend that systemic azole antifungal prophylaxis should be used in all patients receiving chemotherapy or radiotherapy for HIV-associated malignancy (level of evidence 1D), especially those at risk of profound neutropenia and with central venous lines *in situ*. The potential drug interactions of itraconazole, posaconazole and voriconazole may outweigh the enhanced activity against invasive *Aspergillus* and fluconazole is the agent of choice.

12.5 Bacterial prophylaxis

Systemic anticancer therapy and radiotherapy are associated with febrile neutropenia and bacterial sepsis. This risk is increased both by drugs used to treat HIV and its complications and by HIV infection itself [8-12]. Prophylactic GCSF has been shown to reduce the nadir neutrophil count and the duration of neutropenia in people living with HIV [40,41]. In people at risk of neutropenia, other myelosuppressive agents, such as zidovudine and ganciclovir should be avoided.

Prophylactic antibiotics to reduce the incidence of life-threatening bacterial infection in chemotherapy-induced neutropenia remains controversial. Prophylactic fluoroquinolones are advocated for patients undergoing very high-risk chemotherapy who are likely to have prolonged (>1 week) and profound (absolute neutrophil count <0.5 cells/mL) neutropenia including those undergoing allogeneic stem cell transplantation and induction chemotherapy for acute leukaemia [42,43]. Some centres do not follow this practice, because of the concern of selecting antibiotic resistance and other side-effects, and instead have a low threshold for treatment of neutropenic sepsis. In lower-risk patients, the benefits of prophylactic fluoroquinolone have been shown in randomized controlled studies [44,45]; however, the numbers needed to treat to prevent one infection have been high, there are antibiotic-related adverse events, susceptibility to superinfection with *Clostridium difficile* amongst others and risk of selecting antibiotic resistance [46]. We do not recommend routine fluoroquinolone prophylaxis in low-risk patients [47] and the use of co-trimoxazole to prevent PCP may provide some protection against bacterial infection for patients living with HIV (level of evidence 1C).

12.6 Antiviral prophylaxis

The incidence of herpes simplex virus (HSV) and varicella-zoster virus (VZV) seropositivity in people living with HIV is high. The disruption of the cellular immune response associated with HIV and with chemotherapy means reactivation of latent herpes viruses is common. Prophylactic aciclovir or valaciclovir has been shown to reduce viral reactivation in randomized trials of HSV and VZV seropositive individuals undergoing intensive chemotherapy [48-50]. We recommend HSV prophylaxis in people living with HIV with a history of HSV infection who are starting chemotherapy to reduce the incidence and severity of reactivations (level of evidence 1D).

Reactivation of cytomegalovirus infection with conventional chemotherapy is rare and moreover ganciclovir, the most effective agent, causes significant myelosuppression. Prophylaxis against CMV is not recommended even in the context of allogeneic stem cell transplantation where weekly monitoring of CMV replication is recommended for at least 100 days post transplant [51]. Regular monitoring can trigger pre-emptive antiviral therapy and lower rate of CMV infection and mortality but practice varies between centres [52,53].

Active malignant disease is associated with a higher risk of influenza, parainfluenza and respiratory syncytial virus (RSV) infection. Although vaccine response can be highly variable and generally low in people with cancer [54], annual influenza vaccination is recommended as per the BHIVA OI guidelines (level of evidence 1B) [14]. Optimal timing for immunization has not been established, so vaccination is generally performed at least 2 weeks before chemotherapy starts or at least 1 week after the last cycle [43]. Similarly, people living with

HIV and cancer should be vaccinated against pneumococcus and hepatitis B virus (level of evidence tbc) [55].

At least half the people living with HIV have serum markers of previous hepatitis B virus (HBV) infection [56]. Occult hepatitis B, in which there is viral replication in the absence of surface antigen, is well documented in HIV-positive patients [57,58]. Reactivation of HBV and a rise in HBV DNA can occur at low CD4 counts, and has been documented in both HIV-positive and HIV-negative patients receiving immunosuppressive chemotherapy [59-66]. In one study of HBV surface antigen positive patients treated with chemotherapy for lymphoma who did not receive antiviral prophylaxis, 32% experienced HBV reactivation of whom 41% progressed to fatal fulminant hepatitis [67]. The risk of HBV reactivation appears to be particularly high in patients treated with rituximab containing chemotherapy regimens [68].

The use of prophylactic lamivudine in people at risk of HBV reactivation who were treated for lymphoma with chemotherapy reduces the incidence of HBV reactivation, severe hepatitis and the disruptions to chemotherapy compared to historical controls [69]. A meta-analysis of 14 studies involving a total of 275 at risk patients receiving chemotherapy who were treated with prophylactic lamivudine showed that it reduced the risk of HBV reactivation and HBV-related hepatitis by 80–100% [70].

Patients with antibodies against hepatitis B core antigen (HBcAb) should be treated with prophylactic antivirals in line with BHIVA hepatitis guidelines (level of evidence 1B) [71] and this should be continued for at least 6 months after completion of anticancer therapy [72].

12.7 Recommendations

We recommend that all patients with AIDS defining malignancies should start HAART (level of evidence 1B).

We suggest that all patients with non-AIDS defining malignancies who are due to start chemotherapy or radiotherapy should be started on HAART unless contra-indicated (level of evidence 2C).

We recommend that prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) for those who have a CD4 cell count less than 200 cells/µL (level of evidence 1A) and should be considered at higher levels in all patients starting chemotherapy or radiotherapy (GPP).

Prophylaxis against MAC is recommended for individuals with a CD4 cell count less than 50 cells/µL (level of evidence 1B) and in those whose treatment puts their CD4 count at risk of falling below this level.

We recommend that systemic azole antifungal prophylaxis should be used in all patients receiving chemotherapy or radiotherapy for HIV associated malignancy (level of evidence 1D).

We do not recommend routine fluoroquinolone prophylaxis in low risk patients and the use of co-trimoxazole to prevent PCP may provide some protection against bacterial infection for patients living with HIV (level of evidence 1C).

We recommend HSV prophylaxis in people living with HIV with a history of HSV infection who are starting chemotherapy to reduce the incidence and severity of reactivations (level of evidence 1D).

We recommend annual influenza vaccination (level of evidence 1B).

We recommend vaccination against pneumococcus and hepatitis B virus (level of evidence tbc).

Patients with antibodies against hepatitis B core antigen (HBcAb) should be treated with prophylactic antivirals in line with BHIVA hepatitis guidelines (level of evidence 1B).

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