

aids treatment update

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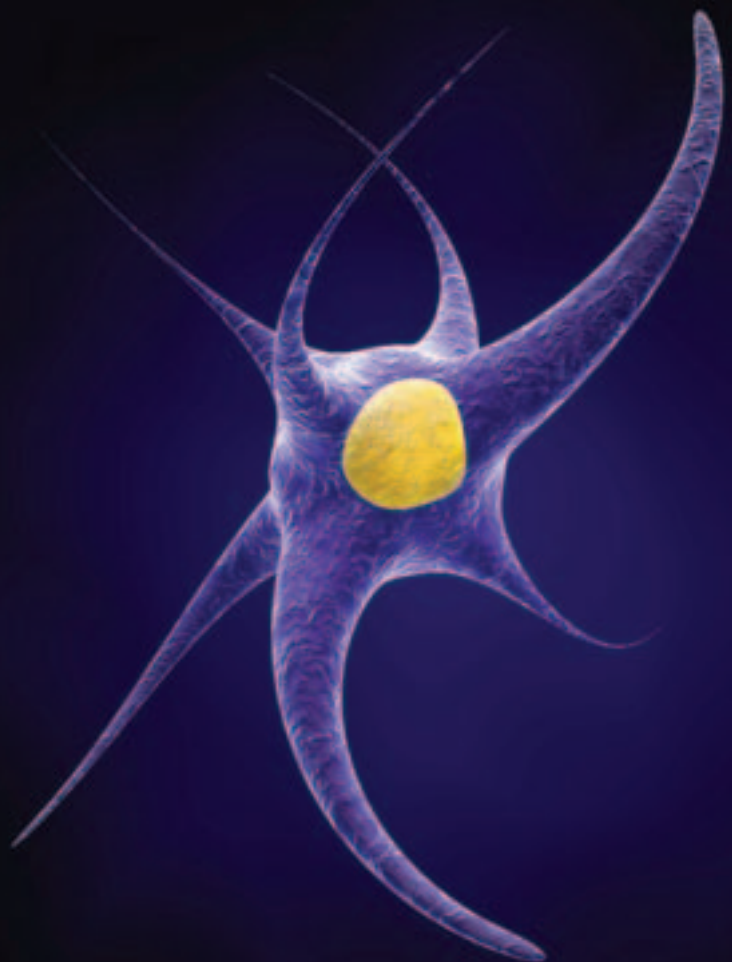
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in this issue

At first I felt reluctant to focus on cancer in my last issue as guest editor, particularly during the festive season. But cancer has been a big part of 2007. We've had studies showing an increased risk of many cancers for those with HIV, a new vaccine targeting cancer-causing viruses and new HIV and cancer guidelines from the British HIV Association (BHIVA). All this news warrants our attention.

So is *ATU* December an issue full of bad news? There's no doubt that malignancies will be an important part of future research into our long-term health - cancer is a modern challenge for everyone, HIV-positive or -negative. However, just over ten years ago we weren't living long enough to worry about most of these cancers so the new concerns are also testament to the longer lives we are living.

We may be at a greater risk of some cancers but we also have our health more closely monitored than the health of many HIV-negative individuals. If we are aware of the increased risks we can do everything we can to prevent cancer from occurring, or at the very least get an early diagnosis and treatment.

For each new challenge we face, there are new measures in place, like the new BHIVA guidelines, to help us get the best possible treatment. So rather than being overly concerned about these risks, it's better to feel empowered. By staying informed, you can do your best to ensure your future is as healthy as possible.

page 2 As with any illness, a dual diagnosis of cancer and HIV affects everyone differently. *Upfront* takes a look at the experiences of patients dual diagnosis clinic to help uncover the some of the challenges they face.

page 4 With an abundance of new data on the increased risks of cancer for people with HIV, some burning questions have arisen about our future health. In *HIV & cancer Q&A ATU* asks Professor Mark Bower where the risks arise and if prevention is possible.

page 8 The skin lesions of Kaposi's sarcoma gave HIV a stigmatising, visual sign of ill-health. With headline-grabbing reports of this emergence of this AIDS-defining cancer in people doing well on antiretrovirals, should we be anxious?

page 12 *News in brief* is dominated by reports from The UK Collaborative HIV Cohort (CHIC) Study Steering Committee.

page 14 Introduction of a new vaccine against a cancer-causing virus was bound to stir up debate, particularly where the virus is sexually transmitted. With the vaccine being introduced only to young girls, people have been left wondering if they should get the jab. In *Cancer protection* we ask if there's a possibility of reducing our cancer risk, and if we should be taking up the offer of private prescriptions despite a lack of clinical evidence.



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coping with a dual diagnosis

by Rob Dawson

Cancer has become one of the major health issues of the 21st century, with approximately 2% - around 1.2 million people - of the UK population living with a cancer diagnosis.¹

The rates for some cancers could be higher when HIV is also in the picture; over the past few months many studies have suggested that non-AIDS-defining cancers are on the rise in people with HIV.^{2,3}

Like HIV, a cancer diagnosis affects people differently, with many factors determining how we will cope with the news. In a bid to understand the experiences of a life with a dual diagnosis of HIV and cancer, Nigel Dodds, a Lead Nurse in the Royal Marsden Hospital, conducted some insightful interviews with patients attending a dual diagnosis clinic at a central London hospital.⁴

What a difference a decade makes

The views and thoughts of the ten participants interviewed varied greatly depending on when they received their HIV diagnosis. An HIV diagnosis over ten years ago was accompanied with greater fear and a shorter life expectancy than a recent diagnosis, due to today's more effective antiretrovirals.

Colin had been diagnosed HIV-positive in 1985. "When they told me, it was like, total shock, because I didn't know anything about HIV. And at that time it was scary because that's when HIV was 'the thing' ... I thought, any minute I'm going to die," he said.

However, Mark's relatively recent HIV diagnosis gave him a different perspective. "Psychologically it's a bit of a blow, but you know... worse things happen. There are so many worse diseases that you can get, other than HIV."

This shift in the way some of us see HIV has given a cancer diagnosis a greater emphasis than in previous years. AIDS-defining cancers were common in the early years of the epidemic and many people diagnosed with HIV were forced to face their mortality head on. Today, many people are doing well on their anti-HIV drugs, which means that a cancer diagnosis can be all the more shocking.

One interviewee commented, "being told that you have cancer is the worst thing, much worse than being told you have HIV."

Many also felt a greater loss of control from the cancer diagnosis than from the diagnosis of HIV: "Before now I dealt with HIV by believing that I can manage it. Now I don't feel like I've got any control. It's like, 'this is what you've got and this is what we're going to do because this is the treatment and that's it.'"

Stigma

When it came to stigma, though, HIV still caused more concern than the cancer diagnosis: "I've told everyone about [my cancer diagnosis] because you get sympathy for having cancer don't you... people just think you deserve to get HIV, like you're a 'guilty' victim, whereas with cancer

you're an 'innocent' victim."

One response did suggest that our battle against HIV-related stigma is having a positive effect: "People around me have been so supportive, I couldn't have asked for a better support network... My attitude was, if they don't like it, then that's their problem."

A complex picture

The interviews paint a complex picture of a dual diagnosis. For those living with HIV, a cancer diagnosis is likely to be accompanied by fear and uncertainty. However, some may find it easier to seek support from friends and family than they did with an HIV diagnosis. While the attitudes of others may be one of the greatest challenges of living with HIV, the challenges of cancer seem to be linked to uncertainty and a loss of control.

However, a recent report from the World Cancer Research Fund⁵ suggests that some control is in our grasp.

Commenting on the report to the BBC, Professor Martin Wiseman, one of the authors said, "Cancer is not a fate, it is a matter of risk, and you can adjust those risks by how you behave. It is very important that people feel that they are in control of what they do."

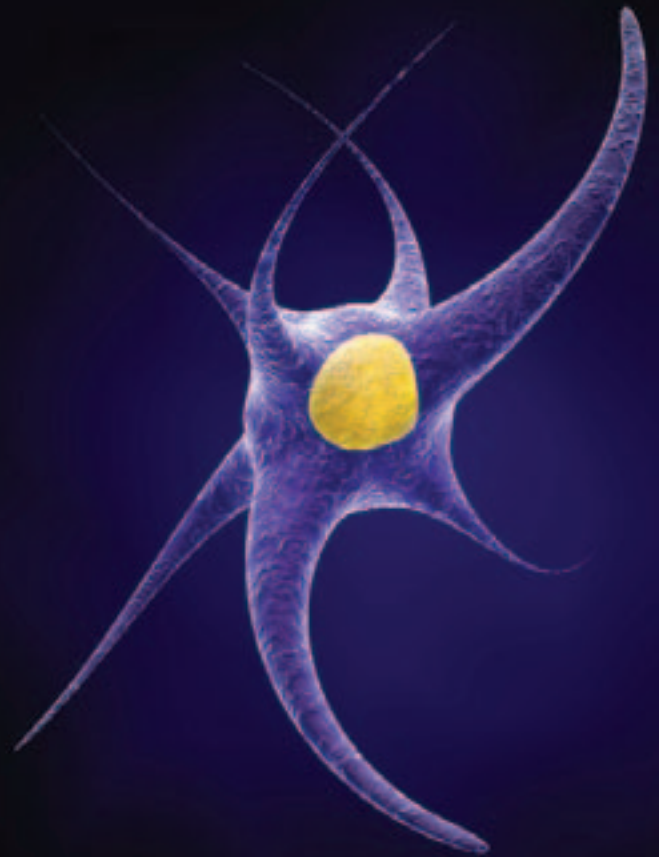
Their message is that not all cases of cancer are down to 'fate', but something that could be in our power to prevent. While this may not always be the case, improving our lifestyle by making it healthier, sure seems worth a try.



hiv & cancer

Q&A with Professor Mark Bower

by Edwin J Bernard



Last month, *ATU* welcomed the arrival of new guidelines from the British HIV Association¹ (BHIVA) on the management of cancer in people with HIV. This summer several new studies were either published², or presented at major conferences³, suggesting that, as we live longer with HIV, the more likely we are to be diagnosed with a wide variety of cancers. In fact, these non-AIDS-defining cancers are now more common than the three AIDS-defining cancers - Kaposi's sarcoma (KS), Non-Hodgkin's lymphoma, and invasive cervical cancer.⁴ (see *Defining cancers* for further details)

This can make for depressing reading: who really wants to think about the possibility that, even with HIV apparently under control (thanks to our regimen of anti-HIV drugs), we may be struck down with another life threatening, stigmatising illness without any warning? After all, it is hard to deny that a dual diagnosis of cancer on top of HIV can be overwhelming, both practically and emotionally, and that it might be easier not think about it unless - or until - it happens to you.

So should our increased risk of cancer simply be something we blithely ignore (thinking there is little we can do about it) or is it possible to channel

this knowledge into some positive action? Might it be possible to prevent some cancers occurring in the first place? What can we, and our doctors, do to make sure we get an early enough diagnosis to ensure the best possible outcome? What can we do to feel somewhat more in control of a cancer diagnosis?

To try and get some answers to these difficult questions, we spoke with Professor Mark Bower, of London's Chelsea and Westminster Hospital, one of the UK's most eminent HIV and cancer experts, who served as lead author on BHIVA's HIV and cancer guidelines.

ATU: Many of us are likely to be in the fortunate position of no longer having to struggle with an HIV diagnosis, and probably feel as if we have our HIV under control. We're living longer, and ageing, with HIV. However, both HIV and ageing increase our risk for many cancers. The main recommendation in the guidelines that helps us feel like we have some control over the likelihood of getting cancer is that we should give up smoking. But are there other things that people with HIV can do? Obviously, we can't help but age, but what else can we do that may actually make the odds work in our favour?

Mark Bower: Apart from making sure that you increase your CD4 count and maintain a viral load that is 'undetectable', there are quite a few things someone with HIV can do to reduce their risk of cancer. Actually, it's the same advice we give to HIV-negative people. So, quitting smoking; eating five fruits and vegetables a day; getting plenty of exercise and staying at a healthy weight; reducing your alcohol intake; not burning in the sun and wearing some protection; making sure you have your hepatitis B vaccinations... all those things can make a difference and help protect you from various kinds of cancers.

ATU: Some of the studies you refer to in the BHIVA guidelines suggest that many of the cancers tended to be diagnosed later in people with HIV than in the general population. In theory you would think that, since a diagnosed HIV-positive person sees their doctor far more regularly than someone without a chronic health condition, cancers would be picked up earlier not later. Is it because people in these studies were being diagnosed with HIV late (and therefore their cancer was diagnosed late, too), or is cancer generally more aggressive in HIV-positive people?

MB: Actually that's quite a difficult thing to tease out from the data. Many of the studies we refer to include a lot of people who were diagnosed late with HIV, with advanced disease, and some of the studies included people who had poor access to health services in general. It used to be said that

AIDS-defining cancers, particularly cervical cancer and Non-Hodgkin's lymphoma, were more aggressive in people with HIV. But, actually, we now think that is not necessarily true.

ATU: So, if someone is diagnosed with HIV and is seeing a doctor regularly, is there an argument for more cancer awareness amongst both HIV specialists and the GPs that are being asked to look after HIV-positive patients' other health concerns. Should they - and we - be more proactive in checking for signs of cancer?

MB: I think that HIV doctors and GPs do need to be vigilant when it comes to cancer screening in HIV-positive people; probably more so than in HIV-negative people. Since the lung cancer risk in someone who is HIV-positive is perhaps double of someone who is HIV-negative, perhaps they would need to be twice as vigilant, and twice as enthusiastic about helping you to stop smoking!

ATU: What do you think about people doing self-examinations?

MB: It makes good sense to check for some of the warning signs of some cancers, such as a sore that doesn't heal; a lump in the breast or testicle; unusual pain or bleeding. I would say that it is unusual for a doctor to notice KS on the skin of their patient before a patient has pointed it out to them. If you think something is wrong, then tell your HIV doctor or your GP. More often than not, though, enlarged lymph glands will not be lymphoma, but it may well be something else that still needs treating.

ATU: One of the recommendations that you made in the guidelines was that once someone has been diagnosed with cancer they should be referred to a hospital that has developed expertise in the management of HIV and cancer. You specifically say these hospitals should have at least 500 HIV-positive patients, but would it perhaps be fairer to say that your recommendation is less about absolute numbers and more about the quality of care, and the quality of the relationship and communication between the HIV doctors and the cancer doctors?

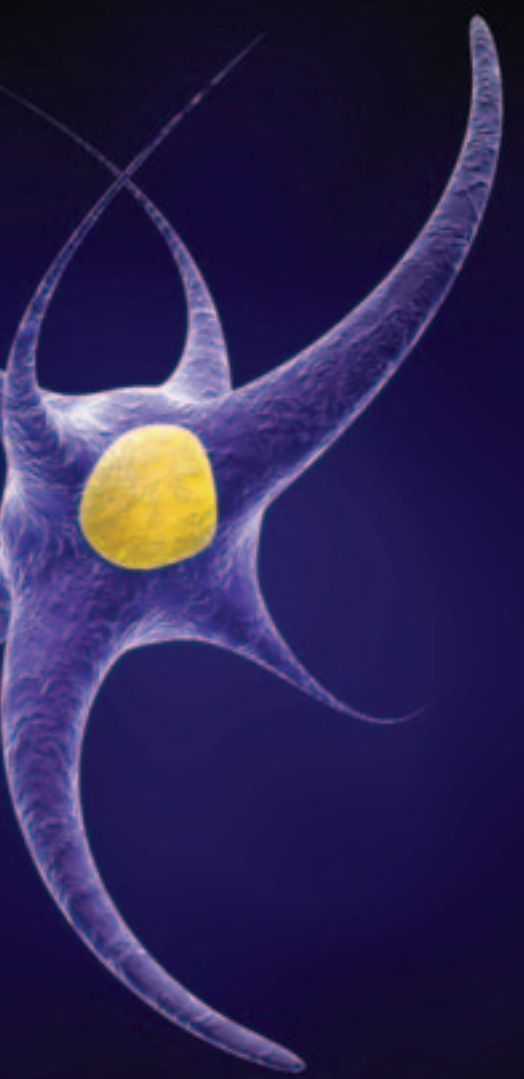
MB: I agree that expertise and communication is key, if you are going to have the best possible outcome. I feel strongly that the chances of you living, if you have HIV-associated lymphoma, for example, is greater if you are treated by a centre where both the HIV and the cancer physicians treat a large number of patients with this diagnosis. It works very well here in north London, where HIV doctors at the various HIV treatment centres have centralised all the management of patients with HIV and cancer so that they are all referred here, at the Chelsea and Westminster. The HIV doctors know that we don't 'steal' these patients' HIV care for the long-term; we treat their HIV and their cancer while there are problems. And when they are in remission they go back to their usual HIV doctor. In order for this to work, there had to be transparency and honesty in the relationship, but it's worked really well for the clinicians.

ATU: Does it work well for the patients?

MB: It probably works well for their health, and for their survival. The question is whether the geography works, because the travelling could be an issue. However, I have patients who come from all over the country, not just from north London, but some who travel down from Scotland, others from the north of England, or the southern counties, to see us for the management of their HIV-related malignancies. Although the travelling isn't ideal, you have to ask yourself: am I getting a better service than if I were seen locally? It's important to remember that if you are entitled to NHS care, you are entitled to seek treatment at *any* centre, not just your local hospital.

ATU: I agree that there are ways to be empowered even with something as disempowering as a dual diagnosis of HIV and cancer. It's also important to remember that you are entitled to ask for a second opinion if you're not happy with whomever you're seeing, and that you won't be penalised in any way if you do.

MB: Well quite honestly, it's as reassuring to the doctor as it is to the patient, and I'm very, very enthusiastic



about second opinions. Of course, it's usually very reassuring to the patient if two different doctors agree on a diagnosis and treatment. But it's very important when seeking a second opinion that you take with you all of your medical reports and tests that have been done so far - like the scan, or the histology report - so that the doctor from whom you're seeking a second opinion is able to furnish you with a fully informed opinion.

ATU: I'd like to compare and contrast cervical cancer (and its precursor, CIN) with anal cancer (and its precursor, AIN). Both are seen more commonly in HIV-positive people, and both are caused by certain strains of the same virus, HPV. Yet cervical cancer is an AIDS-defining cancer and anal cancer is a non-AIDS-defining cancer. And although there has been a national programme to screen women for cervical cancer for many years, there isn't the equivalent for gay men and anal cancer. Why don't BHIVA's guidelines recommend screening for anal cancer?

MB: Screening for anal cancer is incredibly controversial. The subject had already been covered in BHIVA's Reproductive and Sexual Health guidelines⁵ and so another analysis was outside the remit of our guidelines: rather, we focus on the treatment of CIN/cervical cancer and AIN/anal cancer. My interpretation of the problems that we have with establishing recommendations about screening for anal cancer, or rather for its precursor AIN, is that we do not have a reliable intervention that has been shown to reduce the risk of you getting anal cancer. Now, you may very well argue that they didn't have a reliable intervention to prevent CIN becoming cervical cancer, either, when they introduced cervical cancer screening 40 years ago. The incidence of invasive cervical cancer in women before the introduction of screening was about the same as the current incidence of invasive anal cancer in gay men. But there's no consensus on how to treat AIN and proving that any particular treatment reduces your risk of anal cancer would involve an

enormous study that nobody seems to have the enthusiasm to undertake.

ATU: If screening for anal cancer is not going to happen any time soon, what can we hope for in the future?

MB: Clearly what we should be looking at more carefully is anti-HPV vaccination. Currently, however, there are no data on whether the HPV vaccine gives effective protection in women with HIV and we don't yet know whether it's going to give any protection at all in men, HIV-positive or not. The other complicating factor is that in the anal canal of HIV-positive gay men, there appear to be very frequently a large number of different genotypes of HPV present. Some of these are high risk, some are low risk, and others are of an undetermined risk. The two currently available vaccines are primed to work against only two or four HPV genotypes, and this is unlikely to give you cross-protection between other HPV genotypes. There are studies underway in both HIV-positive women and in men, and it's sensible to wait for the results before considering the vaccine.

ATU: I'd like to close by focusing on some good news. You mentioned earlier that even though we used to think that cancers were more aggressive in HIV-positive people, they might not be; that an HIV-positive person may now have just as much of a chance of remission and survival as an HIV-negative person. Has that been your experience?

MB: I think that it does look as though survival in my HIV-positive patients with non-Hodgkin's lymphoma certainly, and Hodgkin's disease, too, is approaching the same survival as the general population. That is a testament not only to the patients' resilience, but also to the HIV and cancer doctors who are being more proactive than before, treating HIV-positive patients with curative intent despite their immunosuppression. People are surviving both HIV and cancer.

ten things you can do to reduce your cancer risk

- 1 Start - and stay on - anti-HIV treatment well before your CD4 count hits 200 cells/mm³.
- 2 Quit smoking.
- 3 Make sure you are vaccinated against hepatitis B, and/or diagnosed and treated for hepatitis B or C infection.
- 4 Practice safer sex to reduce your risk of acquiring other (or more) viruses associated with cancer, such as HPV.
- 5 Eat a wide variety of foods, including foods that contain vitamins and dietary fibre.
- 6 Maintain a healthy weight (not too fat or thin) through diet and exercise.
- 7 Avoid (or reduce your intake of) recreational drugs and don't regularly overindulge alcohol (i.e. binge-drinking). If you have chronic liver disease caused by hepatitis B or C, don't drink alcohol at all.
- 8 Protect yourself from the sun, and always use a sunscreen over SPF15 if you do sunbathe.
- 9 Check yourself for: new or bleeding 'moles' or sores that don't heal; unusual lumps in the neck, under the arms, breast, testicle or groin; changes in bowel or bladder habits.
- 10 Ask your doctor if you should be screened or checked for cervical or anal cancer, breast cancer (for women), or prostate cancer (for men).

defining cancers

Before effective HIV treatments, people with very low CD4 counts (below 200 cells/mm³) were often diagnosed with one of three kinds of cancer, known as **AIDS-defining cancers**:

Kaposi's sarcoma (KS): associated with a member of the family of herpes viruses (Kaposi's Sarcoma-associated Herpes Virus, or KSHV), this cancer is known for its red-purple skin lesions. KS can be life-threatening if it spreads to internal organs, such as the intestines or lungs.

Non-Hodgkin's lymphoma (NHL): associated with Epstein Barr Virus (EBV), there are actually more than 30 different kinds of non-Hodgkin's lymphoma. This cancer affects the lymphatic system - white blood cells that are part of the immune system.

Invasive cervical cancer: associated with some variations of the virus that can cause genital warts (human papilloma virus; HPV). Women with HIV and low CD4 counts are at much higher risk than women without HIV for this cancer.

Doctors are now finding that some cancers are being seen more commonly than their HIV-negative counterparts in HIV-positive people with high CD4 counts (above 200 cells/mm³). **Non-AIDS-defining cancers** include:

Lung cancer: this is the most common non-AIDS-defining cancer in people with HIV. Associated with smoking, the risk is lowered if you stop smoking, but is still higher than in HIV-negative non-smokers.

Hodgkin's lymphoma: is another cancer that affects the lymphatic system. The differences between Hodgkin's and non-Hodgkin's lymphomas are due to the specific blood cells involved - Hodgkin's disease affects B lymphocytes.

Anal cancer: like cervical cancer, this is associated with some variations of the virus that can cause genital warts (human papilloma virus; HPV). It is seen most commonly in gay men; and HIV-positive gay men are at the highest risk, although this cancer can affect anyone with HIV, even if they haven't been the receptive partner during anal sex.

Liver cancer: this is associated with chronic infection with one of two hepatitis viruses, hepatitis B and hepatitis C. HIV-positive people are more likely to progress to liver cancer faster than their HIV-negative counterparts if the hepatitis is not effectively treated.

Skin cancers: Although KS is the skin cancer most associated with HIV, other skin cancers, such as basal cell carcinoma, and malignant melanoma, are more common in HIV-positive people than their HIV-negative counterparts.

Stigma can be one of the greatest challenges of living with HIV, but thanks to effective and improved combinations of antiretroviral therapy, the visual signs of HIV infection have become less dramatic or even non-existent for many of us. While this does not combat stigma head-on, it helps by allowing us to choose whom we disclose our status to. However, recent reports of Kaposi's sarcoma appearing in those doing well on treatment have left some doctors wondering if one of the oldest stigmatising AIDS labels could be rearing its head again.

The changing signs

If you are newly diagnosed with HIV, concerns about visual symptoms are likely to be minimal. Lipodystrophy (body shape and blood fat changes) is an obvious worry, but today's improved treatments usually means that what can't be prevented can now be controlled. If that fails, we can at least hope to improve our outward appearance with facial fillers like *New Fill*. But for those who have been around the epidemic for some time, lipodystrophy worries will be surpassed by the memory of Kaposi's sarcoma and its skin lesions that were all too common in the early days of AIDS.

Kaposi's sarcoma (KS) was one of the first recognised clinical manifestations of HIV infection in the early 1980s. Unlike most cancers, which start in one place and may then spread to other parts of the body, KS can appear in several parts of the body at the same time, causing many visible lesions. A benign form of KS ('classic KS') had been reported in HIV-negative elderly patients of eastern Mediterranean origin as far back as 1872, but this new KS was different. The KS in HIV-positive people (or those with suppressed immune systems) formed the same red or dark raised blotches but was found to be more aggressive and often fatal. This AIDS-defining

cancer became a classic sign of advanced HIV disease.

KS was shown to be caused by the human herpes virus 8 (HHV8), also known as Kaposi's sarcoma-associated herpes virus (KSHV). While the virus does not always lead to the cancer, genetic material from KSHV can almost always be found in KS lesions¹, including non-HIV-related KS, but is very rare in other body tissues.

Gay cancer

Within the context of HIV infection, KS predominantly affects gay men. The exact reasons why gay men are at a higher risk of KS is debated but it's linked to a greater likelihood of being infected with KSHV. Studies have shown that transmission of KSHV increases with the number of years of regular sex between men, the number of past male sexual partners and a past history of sexually transmitted infections.²

Understanding the gender differences, however, is more complex, though, as KS is more common in African men than women, even where rates of KSHV infection are equal between both sexes. This has led to the hypothesis that sex hormones play some part in determining the likelihood of developing the cancer.

80s aids-cancer

by Rob Dawson

While KS is rare among women in the developed world, it is more common in HIV-positive than in HIV-negative women.^{3,4} However, the viral infection that leads to KS in women can often be linked to unprotected sex with a bisexual man.⁵

Antiretroviral effect

The prevention of KS has benefited from antiretroviral treatment, as highlighted by a recent report on skin cancer from the Fourth International AIDS Society Conference in Sydney.

Data from an American database, which included information on 4,566 HIV-positive participants, showed that skin cancer appears to be more common among HIV-positive compared with HIV-negative people. The incidence in the general HIV-negative US population was determined from cancer registries and recent studies.

However, just over 80% of all the reported skin cancers (the vast majority of which were KS) occurred prior to the introduction of effective triple-combination antiretroviral therapy. Once this HIV therapy had been widely introduced, the incidence of Kaposi's sarcoma declined significantly from 1,590 to 180 cases per 100,000 people, per year.⁶

Similar results have been seen in various other studies. The EuroSIDA

study has reported a dramatic fall in KS incidence in its analysis of over 7000 individuals from Europe, Israel and Argentina. The data showed that the number of KS cases reported among participants in 2003 was less than 10% of the number of cases reported in 1994.⁶ Although KS is rare in women, a similar drop in incidence has also been observed in women.⁴

Potent PIs?

This dramatic reduction of reported KS cases coincided with the widespread introduction of protease inhibitor-based antiretroviral therapy. Doctors noted that the tell-tale lesions often

spontaneously shrank and disappeared in HIV-positive patients on protease inhibitors (PIs), and deaths associated with KS declined substantially.

At first, there was speculation that protease inhibitors had a direct effect on Kaposi's sarcoma independent of their effect on the immune system (perhaps by reducing levels of the causative virus) but a French study published in 2006 found no difference in the rate of KS remission between patients treated with protease inhibitors or an alternative choice of antiretrovirals, non-nucleoside reverse transcriptase inhibitors (NNRTIs).⁸



er resurfaces

Previous studies had also demonstrated that NNRTIs were as effective as protease inhibitors at preventing HIV-related KS^{9,10} and in prolonging time to KS treatment follow-up¹¹.

Even where KS is not prevented, it generally responds well to antiretroviral therapy. KS often significantly improves, and blood levels of KSHV drop dramatically, when antiretroviral therapy is started. This improvement is likely to be due to the restoration of immune function.¹²

KS cluster

With today's combinations of antiretroviral therapy, KS lesions have been seldom seen in the UK, and researchers have focused their attention on adults in sub-Saharan Africa, where antiretrovirals are scarce and KS remains a common malignancy. That was until a letter in the *New England Journal of Medicine*¹³ sparked a series of haunting news stories.

"San Francisco doctors have reported a cluster among gay men of unusual cases of Kaposi's sarcoma, the cancer-like skin disease whose disfiguring purple lesions were a terrifying signature of a bygone era of the AIDS epidemic," wrote *San Francisco Chronicle* reporter, Sabin Russell under the October 12th headline: Unsettling re-emergence of 'gay cancer'.

What caused particular concern was the fact that the reported cases of KS were in HIV-positive men who were doing well on antiretroviral therapy. Nine KS cases seen between 2004 and early 2006 were described in the original letter, all in gay men who were taking potent antiretroviral therapy and had maintained a CD4 cell count of above 300 cells/mm³ with durable viral suppression. By the time news reporters had spoken with the doctors in San Francisco, there were 15 cases in total.

Initial fears of life-threatening cancer seem to be misplaced in this instance. Unlike KS seen in untreated HIV

infection, the cluster of cases seen in San Francisco appear to be more like the classic form of KS described earlier - the kind of Kaposi's sarcoma that is found in countries surrounding the Mediterranean - which is slow to develop or heal, causing little or no pain. None of the patients became physically unwell because of KS, and doctors described it as an 'indolent' form.

The report stated, "the patients have had a relatively indolent course of Kaposi's sarcoma, with no eruptive cutaneous lesions, visceral involvement, or other AIDS-defining illnesses."

But there are differences between the classic and new KS. Whereas the classic KS is not HIV-related and occurs in older men (usually in their 70s), this indolent form was seen in gay men with an average age of 51 who had been diagnosed with HIV infection an average of 18 years ago: in other words aging long-term survivors.

As well as having high CD4 levels, the men in San Francisco had well-preserved immune function when they started antiretroviral therapy. Their lowest ever (or nadir) CD4 cell counts was an average of 340 cells/mm³. None of the men had a history of any other AIDS-defining infections.

A single case of KS in a patient taking successful antiretroviral therapy had been reported previously¹⁴ but this was the first time a cluster of cases had been reported. The doctors believe that they have been able to see this cluster because the city has "a high number of ageing patients who are infected with both HIV and human herpesvirus 8" (the underlying cause of KS).



Protease inhibitors showed once again to have no additional protective benefit over other antiretrovirals; seven of the San Francisco patients received protease inhibitors without improvement in their Kaposi's sarcoma.

"These patients present a clinical and prognostic conundrum" concluded the *New England Journal of Medicine* report, "they are receiving maximal

“Most of the patients that we see with this combination of high CD4 count, undetectable viral load, and newly diagnosed KS, have often been HIV-positive for a number of years. There may be an issue about not just how low your CD4 count is but also how long it has been low.”



antiretroviral therapy yet have persistent Kaposi's sarcoma. This phenomenon may increase in frequency as the HIV-infected population ages, and we recommend that physicians monitor this group carefully."

Whether the 15 confirmed KS cases are a collection of rare events or an indication that this AIDS-defining cancer may occur despite effective treatment, is unclear. The individual cases have no comparison to a greater population so it is impossible to tell if these are 15 cases out of a million or 15 out of 16. However, UK doctors may have clearer answers.

KS in the UK

London's Chelsea and Westminster Hospital examined data from their patients to see if similar KS cases had emerged in the UK. While the data are yet to be peer-reviewed, they provide some startling results.

In this cohort, 389 patients had been diagnosed with HIV-related KS since effective triple-combination antiretroviral therapy became available. Of these, 74 (19%) were on antiretroviral therapy when KS appeared, 28 (7%) had undetectable

HIV viral loads and 18 (5%) also had a CD4 cell count that was above 300 cells/mm³.

These 18 patients would at first appear to mirror the American cases (successfully managing HIV infection but with KS appearing despite this), but there are clear differences. While the US KS report suggests that increasing age and number of years since HIV diagnosis could be important factors, the 18 UK cases did not confirm this. When compared with the rest of the Chelsea and Westminster KS patients, they weren't older and they hadn't had HIV for longer.

Even more surprising was the fact that they did not have better survival. There was no biologically different form of 'indolent' KS, and the patients had the same outcomes as everyone else with both HIV and KS.

Clinical view

While grilling Chelsea and Westminster's Professor Mark Bower for our Cancer Q&A on page four, *ATU* asked what these data mean for those doing well on antiretroviral treatment.

"At the time of diagnosis of KS, a significant minority of our patients have relatively high CD4 counts and amongst them several patients also have undetectable viral loads on effective antiretroviral therapy," said Dr Bower. "Those patients are often relatively difficult to manage. Any form of antiretroviral approach isn't going to work because it's already controlling your HIV, but your immune system is unable to control your KS. I presume it's because during immune re-constitution you failed to re-constitute immune function against KSHV."

The reasons why some people's immune system fails to make an immune response against the virus that can cause KS remain a mystery.

"I don't know the answer to that, and nobody seems to," explained Dr Bower. "Most of the patients that we see with this combination of high CD4 count, undetectable viral load, and newly diagnosed KS, have often been HIV-positive for a number of years. There may be an issue about not just how low your CD4 count is but also how long it has been low."

Cause for concern?

While these cases of KS are creating new challenges for specialist doctors, we haven't seen an emergence of KS anywhere near the levels witnessed 25 years ago. Of the 15 cases in San Francisco, none are experiencing an immediate risk of death or decreased survival.

The fact that antiretroviral therapy will be ineffective in these cases may also cause concern, but other options are available. Patients can often be treated with local measures such as radiation therapy or cryotherapy. Widespread disease, or disease affecting internal organs, is generally treated with systemic therapy such as interferon alpha (also used to treat hepatitis C) or chemotherapy.

The UK data suggest that KS in the patients with high CD4 counts and undetectable viral loads can have a negative effect on survival, but the possibility of KS in otherwise outwardly healthy people with HIV remains rare. Nevertheless, news of the re-emergence of stigmatising visible marks of HIV will no doubt dredge up unsettling memories of the AIDS epidemic for many of us - perhaps mostly due to the possibility of outward signs of HIV. While we need doctors to do their best to combat KS, avoiding visible signs will only reduce stigma for the individual. If we combat stigma at its roots, whole communities could benefit.

hiv therapy

Many patients stay on failing treatment

One in five UK patients remains on a failing regimen for more than a year, and one in ten for more than two years, according to data from the eleventh European AIDS Conference (EACS) in Madrid.

The analysis of the UK Collaborative HIV Cohort (UK-CHIC) also found that only half of those changing therapy due to viral load rebound did so in accordance with the British HIV Association (BHIVA) guidelines. Doctors were less likely to stick to guidelines in recent years.

The study reported on patients starting HIV therapy between the beginning of 1998 and the end of 2004, and specifically the group of patients who experienced virological failure to this first HIV drug regimen. Failure was defined as two or more viral loads over 400 copies/ml within the space of six months.

Thirty-six per cent remained on a failing regimen with a detectable viral load after six months, 21% after a year, and 10% after two years. There was no relationship between the year of failure and the likelihood of a change in therapy. In other words, patients failing in 2004 were no more likely to change therapy than those who failed in 1998.

Presenter Caroline Sabin of the Royal Free and University College Medical School explained that UK-CHIC collects limited information, so the figures were difficult to interpret. Physicians might be adopting a 'wait and see' approach; patients might be reluctant to change; some of the patients might have viral loads which hovered just above detectability; resistance tests may have been unclear or found no resistance.

"However," Sabin added, "these were people on first-line HAART regimens so they shouldn't have to be waiting for new drugs to come along to construct a second-line regimen."

hiv therapy

CD4 gains rarely alter

A study of UK patients presented at the eleventh European AIDS Conference (EACS) found that patients starting antiretroviral therapy gain roughly equal numbers of CD4 cells regardless of their initial count, except for those starting with extremely low or extremely high counts.

Data from the UK-CHIC cohort found that those starting treatment at low counts may never reach normal CD4 levels. This adds to the weight of evidence that starting treatment earlier, before CD4 cell counts fall below 350 cells/mm³ or so, is better than waiting until counts have fallen below 200 cells/mm³.

The data selected were from patients who had started antiretroviral therapy between the beginning of 1998 and the end of 2005 and who had maintained undetectable viral loads from six months after the start of treatment to the end of the study.

The cumulative CD4 increases for each stratum of baseline CD4 cell count were:

Baseline CD4 count	Increase over five years
Under 25	389
25-50	322
50-100	309
100-200	285
200-350	289
350-500	281
Over 500	160

There was relatively little variation in CD4 increases in those in the middle strata, with patients with 25-50 CD4 cells only gaining 40 more CD4 cells than those starting with 350-500 CD4 cells. The eventual CD4 cell count is therefore much more dependent on the baseline count than on variations in the rate of increase while on treatment. Only those starting treatment with counts above 350 cells/mm³ achieved CD4 counts nearing normality for people without HIV.

starting treatment

Start treatment over two years earlier?

In October, *ATU* reported on the potential benefits of starting treatment at higher CD4 cell counts than currently recommended. This was based on, among other studies, UK Collaborative HIV Cohort (UK-CHIC) findings that patients with a CD4 cell count between 350 and 500 cells/mm³ have an increased risk of death compared to patients with a CD4 cell count above 500 cells/mm³.

The UK-CHIC investigators have now turned their focus to the clinical implications of starting treatment earlier. New data have shown that starting antiretroviral therapy when a patient's CD4 cell count is above 500 cells/mm³ would mean that treatment would need to be started two and a half years earlier.

Treatment guidelines are now starting to endorse the initiation of anti-HIV therapy when an individual has a CD4 cell count

around 350 cells/mm³. It remains uncertain, however, if there would be any additional benefit starting antiretroviral therapy at an even higher CD4 cell count. To assess any benefits, a randomised controlled clinical trial would be needed and the UK-CHIC investigators hope that these new data will help lead the way. They suggest that the results of their studies support the design of a trial to compare the outcomes of patients who start anti-HIV treatment with CD4 cell counts of 500 cells/mm³ versus 350 cells/mm³. Would these additional years of treatment have any benefit? Their earlier research has shown that, "for untreated patients with a CD4 cell count in the 350 - 500 cells/mm³ range, the rate of AIDS or death is approximately 2.5 per 100 person years, which translates to a predicted 6.1% cumulative risk over the 2.5 years spent with a CD4 cell count in this range while deferring antiretroviral therapy."



adherence



No adherence benefit for once-daily nevirapine

Patients who take once-daily antiretroviral therapy based upon nevirapine (*Viramune*) do not have better adherence to their treatment than patients who take the drug twice daily, according to a French study. The study also found that patients who took once-daily therapy were four times more likely to miss taking their anti-HIV treatment for two or more consecutive days, a risk factor for the development of drug-resistant virus.

For many patients, rigorous adherence to antiretrovirals is a challenge. Before the study began, the investigators in France thought that switching to once-daily treatment would improve adherence amongst patients who had initiated anti-HIV therapy with a regimen that included twice-daily doses of the

non-nucleoside reverse transcriptase inhibitor (NNRTI), nevirapine. Adherence was electronically monitored and blood tests were used to check plasma levels of nevirapine.

Adherence was a non-significant 0.5% better amongst patients taking once-daily nevirapine but the odds of a treatment-free day were increased by 70% for this group. Once-daily dosing was also significantly associated with having two or more consecutive days without HIV therapy. This length of interruption increased the risk of drug-resistant HIV emerging.

"We found no evidence of improved adherence rate with once-daily dosing", write the investigators, adding, "once-daily dosing was associated with an increased number of drug interruptions."

cancer protection

should we be getting the anti-hpv jab? By Rob Dawson

In September this year, the first vaccine against human papilloma virus (HPV) was licensed for use in the UK. The link between HPV and cancers which are more common in people living with HIV has led to speculation that the jab should be part of our long-term care. But are we creating a climate of fear by reacting to the media hype?

HPV and cancer

Some reports suggest that around eight out of ten people (80%) in the UK will be infected with HPV at some time during their lifetime.¹ With over 100 types of HPV, around 40 of which are sexually acquired, there are varying consequences of infection. For some the virus is asymptomatic, for others it can lead to cancer.

The sexually acquired viruses can be divided into low and high risk types. The types classified as 'high risk' have been the main motivator for an HPV vaccine with HPV types 16 and 18 accounting for around 70% of cervical and anal cancers. The low risk types can cause health problems too, such as genital or anal warts, benign lesions and persistent infection.

The new HPV vaccine called *Gardasil* is a quadrivalent vaccine which means it protects against four types of HPV. Large scale, multi-centre clinical trials in women have shown that *Gardasil* can prevent close to 100% of high-grade pre-cancer or non-invasive cancer of the cervix caused by HPV 16 and 18 and 99% of genital warts caused by HPV types 6 and 11.² No serious adverse effects have been associated with the vaccine and only

mild symptoms were seen at the injection site.

As HPV 16 and 18 account for around 70% of cervical cancers, the Department of Health have stated that widespread vaccination of girls aged around 12-13 years could reduce cases of cervical cancer by up to 70 per cent.³

The government has already announced that girls aged 12-13 will be vaccinated from September 2008, with a 'catch-up campaign' offering the vaccine to girls aged up to 18, but what about the boys?

Vaccination for men

While the benefits of vaccinating men have yet to be proven, there has been much debate. Not only would vaccinating men help protect their sexual partners from HPV but it could potentially help to reduce anal cancers and genital warts. While clinical trials are needed to answer these questions, the general public seems to be drawing its own conclusions.

In November, men's health website '*Male Health*' conducted a snap survey to see whether its readers thought that boys should receive the HPV vaccine as well as girls. The majority thought they should. Of those that responded, 55% of men and 88% of women said that boys should be vaccinated against HPV.⁴

HPV and HIV

The same questions are being asked about vaccinations for those with HIV. Women with HIV and low CD4 counts are at much higher risk of cervical cancer than women without HIV⁵ and, while anal cancer remains relatively rare, it does occur more frequently in HIV-positive gay men.⁶

A study of HIV-positive gay men in San Francisco found that 95% had anal HPV infection, and more than 50% had grade 2 or 3 anal intraepithelial neoplasia (AIN), which, untreated, may lead to anal cancer.⁷ The study also confirmed other reports which suggest that antiretroviral therapy is not protective of AIN, and that anal cancer can be difficult to treat.⁶

The price of fear

The case for HPV vaccination in those with HIV may sound concrete but without safety trials it's impossible to weigh the costs against the benefits. Nevertheless, an article in the October edition of *Positive Nation* showed that a private health clinic, Freedom Health, was willing to take that gamble. They state that "the vaccine is not live and should therefore be safe," and that "it is available as a private, off licence prescription for men" - at a price.

Even before the cost of private care, the Health Protection Agency (HPA) has suggested that the vaccine is very expensive - three doses are required at a cost of £241.50.⁷ Cost of the vaccine isn't the only issue; you'll also need to pay for a swab to determine if you already have HPV. To ensure maximum benefit and protection from this vaccine, it is necessary to administer it before the onset of sexual activity. If you've already been infected with the types of HPV that the vaccine can protect you against, there is no benefit to being vaccinated. There's also the uncertainty of effect at different CD4 levels to consider. However, some investigators continue to argue the case for HPV vaccination of those with HIV. Research presented at this year's International AIDS Society Conference



in Sydney, found that 41% of HIV-positive gay men were infected with the high risk HPV strains 16 and 18.⁹ Given the prevalence of HPV 16 and 18 infection, the investigators believe that mass HPV vaccination of gay men would be justified and could prevent many cases of anal cancer.

Future vaccines

While the availability of an HPV vaccine is exciting news, important questions need answering before a programme of blanket HPV vaccination can be introduced. The fact remains that the vaccine has not yet been licensed for use in men or those with HIV and effectiveness in either group is not clinically proven. As a recent review of available data concluded, "the safety and efficacy of human papilloma virus vaccines in individuals with HIV need to be assessed".¹⁰ Investigations are needed to ensure that the benefits outweigh the costs, both to our pockets and our health.

Even if the majority of us are probably already infected with HPV, it's important to remember that it doesn't necessarily mean that cancer is on the cards. Even the high risk types do not cause cancer in everyone; other factors play a part. If the HPV publicity still causes concern, consider the developments in therapeutic HPV vaccines to treat established HPV infections and HPV-associated cancers. If these vaccines make their way to a clinic near you, you can be sure that *ATU* will be there to update you on the news. ■

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