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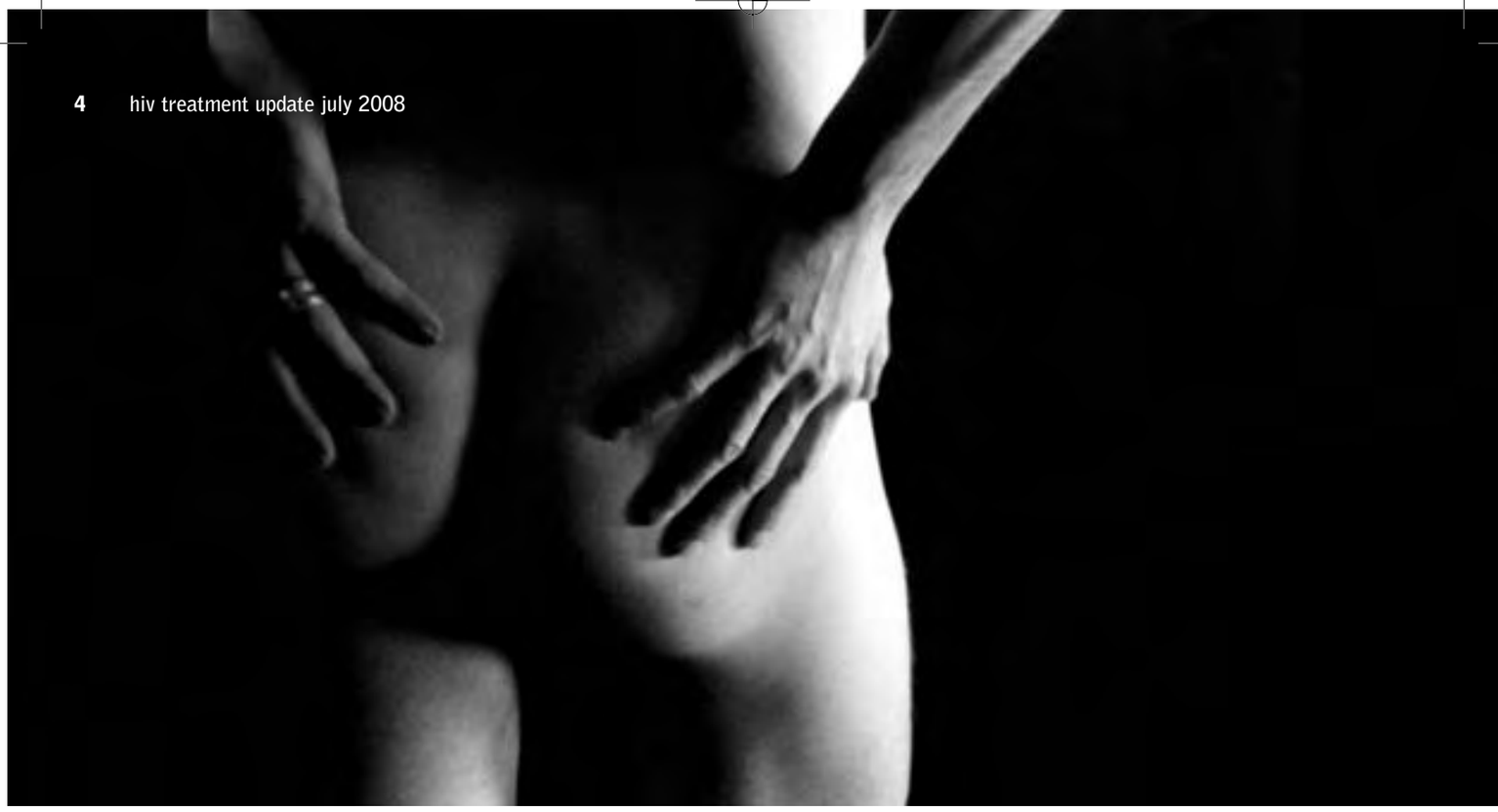
hiv treatment update



In May, the largest analysis ever undertaken of cancer incidence trends among HIV-positive individuals in the United States[1] found that nine non-AIDS-defining cancers are more likely to be seen in HIV-positive individuals than in the general population.

Notably, the study found that between 2000 and 2003 (the most recent time period analysed), anal cancer was almost 60 times more common in HIV-positive individuals than in the general population. Only Kaposi's sarcoma (KS) (one of the three cancers that are labelled AIDS-defining, along with non-Hodgkin's lymphoma (NHL) and cervical cancer) had a greater likelihood of occuring in HIV-positive people. (KS is 112 times more likely to be found in HIV-positive people than in the general population.)

The study also found that anal cancer incidence in 2000-2003 had quadrupled since the period 1992-1995, before potent anti-HIV therapy, whereas the incidence of KS and NHL had fallen by more than 80% in the same period.

Interestingly, the incidence of cervical cancer – which, like anal cancer, is caused by human papilloma virus (HPV), the virus that causes genital and anal warts – had remained virtually the same over the entire study period, strongly suggesting that anti-HIV treatment had no discernible effect on this HPV-associated disease. Given the parallels between cervical and anal cancer, some experts argue that anal cancer should now be redefined as an AIDS-defining cancer.

> "HIV-positive people (not just gay men, so that includes men and women who haven't ever had anal sex) are much more likely to have anal cancer than the general population."

Is there any good news?

So, incidence of anal cancer is rising; anti-HIV treatment doesn't seem to have any effect (and actually now allows us to live long enough for HPV infection to develop into anal cancer); and HIV-positive people (not just gay men, so that includes men and women who haven't ever had anal sex) are much more likely to have anal cancer than the general population. Is there any good news?

Well, the study found that anal cancer

- is the sixth most common cancer in HIV-positive people (AIDS-defining cancers remain the top three);
- is the third most common non-AIDS-defining cancer, after breast and lung cancer; and
- is still relatively uncommon, affecting one HIV-positive person out of every 1278 in the years between 2000 and 2003.

So it appears that the risk of getting anal cancer is still very low. Despite that, people are dying every year of a disease that some experts strongly believe is preventable and is definitely curable if diagnosed early enough. The problem is that, in the absence of screening programmes, even with the best available care, such as at London's Chelsea and Westminster, anal cancer is often diagnosed late, resulting in a five-year disease-free survival rate of only 66%.[2]

A high proportion of those diagnosed with anal cancer are men with a history of anal intercourse, although women are at increased risk, too (in fact, in the general population, more

giving anal cancer the finger

what every hiv-positive person should know about this increasingly common – and preventable – disease, by Edwin J Bernard

women than men are diagnosed with anal cancer). HIV-positive people are getting anal cancer much younger, however. In the general population, anal cancer usually occurs in people over 60. For HIV-positive men and women, the average age of diagnosis is in the early 40s.

Although this latest US study is worrying, the increased incidence of anal cancer is not exactly breaking news – studies from all over the developed world, including the United Kingdom – have been telling different parts of the anal cancer story for the past few years.

We first addressed the issue back in September 2002 (*ATU* 117), when we interviewed Professor Joel Palefsky of the University of California, San Francisco, who is a leading authority on HIV, HPV and anal cancer. Having seen a dramatic increase in both anal cancer and pre-cancerous anal lesions – also known as 'anal intraepithelial neoplasia' (AIN) – in his own San Francisco clinic, he was way ahead of his time, calling for anal cancer and AIN screening programmes for HIV-positive people and HIV-negative gay men from the start of the decade.

We revisited HPV and anal cancer in November 2005 (*ATU* 151), by which time Dr Paul Fox of London's Chelsea & Westminster and Ealing Hospitals (who is one of a handful of clinicians in the UK who does offer patients AIN cancer screening) was also calling for anal cancer screening for all HIV-positive people and HIV-negative gay men.

At the British HIV Association (BHIVA) conference in Belfast in April, two other UK HIV clinics (Homerton Hospital in East London and Edinburgh Royal Infirmary) presented data on their pilot screening programmes. At Homerton, they found that anal Pap smears were most likely to accurately detect pre-cancerous lesions if they were already large and widespread.[3] In Edinburgh, when anal Pap smears were offered to HIV-positive gay men during sexual health check-ups, only 62% accepted. The men who refused also refused all other tests for sexually transmitted infections, say the researchers, because they thought they weren't at risk.[4]

As far as we can discover, these three centres (two in London and one in Scotland) are the only places offering anal cancer and AIN screening programmes in the UK.

"The incidence of anal cancer is unacceptably high. If we had these kinds of rates for cervical cancer in the US or UK, this would be a major concern, and people would want to do something about it."

"The incidence of anal cancer is unacceptably high," Professor Palefsky told the BHIVA conference during his plenary session on screening strategies for cervical and anal cancer. "If we had these kinds of rates for cervical cancer in the US or UK, this would be a major concern, and people would want to do something about it."

Why, then, is there still no national screening programme for anal cancer, or the pre-cancerous lesions that may lead to anal cancer, and what can we do to reduce our risks of dying of anal cancer?

HPV disease

There are more than 200 HPV strains, but only about one-tenth of these commonly infect the genitals or anus HPV types 6 and 11 cause genital warts and are considered 'low risk' for cancer. The most common 'high risk' HPVs are strains 16 and 18, which are implicated in 70% of cases of anal cancer. However, only a very small number of people with anal HPV infection will develop high-grade pre-cancerous lesions, and even fewer will develop anal cancer. See *ATU 151* (downloadable from **aidsmap.com**) for much more detailed information on the links between HPV, warts, and cervical and anal cancer.

Not enough evidence?

Why is it so hard to develop and roll out a simple method of detecting early signs of pre-cancerous changes in the anuses of people with HIV?

After all, anal cancer is a very similar disease to cervical cancer in women. Both cancers are caused by 'high risk' strains of HPV, which progress through various stages (and often regress, too) until, in a small proportion of people, cancer develops. Guidelines recommend that HIV-positive women undergo cervical Pap smears every six months in order to look for pre-cancerous cells, why can't the same be true for anal cancer?

"I think the main reason," Professor Palefsky told the BHIVA Conference, "is that we exist in the era of evidence-based medicine, and I think that's appropriate. We don't have the evidence yet that screening is actually going to reduce the incidence of anal cancer."

Frustratingly, there have been no randomised trials examining the outcomes of anal Pap smears, or which treatments can successfully prevent anal cancer, and so there is no evidence to indicate whether individuals who have had Pap smears have better outcomes than those who do not. What's more, there is still uncertainty surrounding the rate at which pre-cancer progresses to anal cancer in people with HIV.

"Of course," notes Professor Palefsky, "we didn't have that evidence for cervical cancer, either, when we adopted cervical screening [in the 1960s] and it probably would not be in use right now if we were to apply the same standards [to cervical cancer screening as we are now doing to anal cancer screening]."

> "Does treatment of AIN reduce incidence of cancer? Hopefully we'll have those data some time within the next decade or so."

"The fact that we don't have those data yet is the reason why most governmental bodies have not recommended screening," he continued. "I think we're close to answering the first question – that treatment of AIN is possible – but, of course, the gold standard question is this: does treatment of AIN reduce incidence of cancer? Hopefully we'll have those data some time within the next decade or so."

How accurate are anal Pap smears?

There are some other unanswered questions, though, including those concerning the accuracy of anal Pap smears. "We have to take the results [of anal Pap smears, also known as cytology] with a grain of salt," Professor Palefsky told the BHIVA Conference. "In people who have AIN 2 or 3 [pre-cancerous lesions with the highest risk of progressing to cancer] on biopsy, the range of cytology results from the same patient on the same day are quite broad, including patients who have normal cytology."

He also said that when you compared anal Pap smears to biopsies of anal tissue (which tend to be much more accurate), many people thought to have had low-grade AIN actually had high-grade disease. In other words, although anal Pap smears can detect whether there any potential problems, they aren't very good at separating the people at low risk of progressing to cancer from those who are at higher risk.

However, there is good correlation between having high-grade AIN during an anal Pap smear and having high-grade AIN as determined by biopsy. So, noted Professor Palefsky, "if you're looking to prioritise who needs high-resolution anoscopy, then it makes sense to 'scope those with high grade cytology followed by low grade, followed by those with atypical cells."

So, an anal Pap smear can be best described as a general indicator of whether cells in the anus are normal or abnormal. If they are abnormal then further examination is required, usually by high-resolution anoscopy.

Widening the scope

High-resolution anoscopy is the viewing of the lining of the anus using a microscope. A small plastic tube is inserted to make this possible, but – fear not – the microscope remains outside.

"I have to emphasise that this is not an easy technique [for the clinician]," Professor Palefsky told the conference. "It's helpful to have a background in cervical colposcopy [the equivalent test for cervical pre-cancers], but it takes lot of practice for highly accurate results and people who have done both tell me that an anoscopy is more difficult."

> "When people talk about a lack of resources for anal cancer screening, they aren't just talking about money – we also don't have very many people in the UK with enough expertise."

So when we hear people talk about a lack of resources for anal cancer screening, they aren't just talking about money – although that is certainly an issue. The problem is that right now we just don't have very many

people in the UK with enough expertise to accurately diagnose anal pre-cancer.

As Dr Palefsky argues, the chances that an HIV-positive gay man will have an abnormal anal Pap smear are quite high. In the Edinburgh screening programme, for example, one in five of those who had an anal Pap smear had abnormal smears. "If resources were unlimited," he told the conference, "then probably we should dispense with cytology altogether and just 'scope and biopsy everybody. But obviously that's not practical."

Indeed, he later told me that at his San Francisco clinic, even with four highly skilled clinicians, there is a four-month waiting list for high-resolution anoscopy.

Improving treatments

A prerequisite for the setting up of a national anal cancer screening programme is the availability of effective treatment, and although some progress has been made, the effectiveness of the various treatments for pre-cancerous anal cells is still uncertain.

At present, possible options include treatment with topical agents, such as fluorouracil (*Efadix*) or cidofovir (*Vistide*). Imiquimod cream (*Aldara*) appears to be the most successful of these: a recent UK study found a 39% response rate compared to an 8% response rate in people who had no active ingredient in the cream they were given for an average of 19 months.[5] This suggests that even with a placebo, spontaneous resolution of high-grade pre-cancerous lesion is possible in HIV-positive people. On the other hand, even with the best treatments, new lesions can reoccur several years after past success.

There are also physically destructive methods, such as laser vapourisation, trichloroacetic acid and infrared coagulation (IRC), which have better success rates than topical agents, although the possibility of reoccurrence within a few years remains.

Dr Palefsky uses 85% tricloracytic acid to treat individuals "with a few lesions. It's very well tolerated, and can get rid of the lesions after two or three treatments, most of the time," he told the conference. "With bigger lesions, we are very pleased to have a treatment, infrared coagulation, that we think works most of the time. Again, it's very well tolerated – it's done in our office, and most patients go right back to work. We have good data suggesting that two thirds or so – even if HIV-positive with low CD4 counts – will get clearance of high-grade disease after more than one year. That's really good news," he said, "and I think a major step forward for us."

Infrared Coagulation (IRC)

was initially developed to remove tattoos, and treat haemorrhoids and external anal warts. Then a 2005 study[6] from Professor Palefsky's team showed it to be an effective treatment for internal anal warts and high-grade pre-cancers. The treatment involves the application of a heat-guided probe directly to the lesions to create a small blister, which can than be removed. Lidocaine is used as a local anaesthetic to reduce discomfort during the procedure, which can take up to an hour, and in most cases the treatment can be completed in just one session. The risk of complications is very low, although some pain, requiring painkillers, will be felt for a few days following the procedure and bleeding can occur with bowel movements for up to three weeks.

"But even if patients come in with very widespread [pre-cancerous lesions], there are still benefits to watching them very carefully," he said. "Here you're not going to cure the patient of high grade disease but you're going to watch them to see that they don't develop cancer and if they do, you can pounce on it quickly."

The earlier the better

The benefits of catching anal cancer early are clear. Dr Paul Fox tells *HTU* that, "if you catch it early, the five-year survival rate is going to be higher than 90%." Diagnosing anal cancer later – once it has become invasive cancer – means a combination of chemotherapy and radiation therapy is required, which can cause many debilitating side-effects, such as scarring of the tissues around the anus caused by the radiotherapy, which, notes Dr Fox, is "likely to make anal sex unappealing for both parties".

Fortunately, Professor Palefsky's team have been doing studies "where we've been following people [with high-grade, widespread AIN] every four months, and when they did develop cancer, we knew it was very early cancer. We had 19 patients and we sent them to our surgical colleagues to have the cancer excised." Although none died, five did have reoccurrence of their cancer, but only two required chemo-radiation, and none required a colostomy. "We did our patients a service," he told the conference, "but I will point out that a lot of them went on to have reoccurring high grade [pre-cancerous lesions], so they do require continued monitoring even after the removal of their cancer."

Giving anal cancer the finger

If there was one take-home message Professor Palefsky wanted to impart to his audience of UK HIV clinicians, it was that there is a difference between anal pre-cancer screening tests and looking for anal cancer.

"The best cancer screening tool is your finger."

"The most important thing, especially if you haven't yet set up anal screening, is to make sure that your patients don't die of cancer," he said. "And the best cancer screening tool is your finger. Do a digital rectal exam: it's the best way to detect cancer because you can feel things that you can't see doing cytology or anoscopy." (There's more about the digital rectal exam over the next few pages).

anal cancer Q&A

HIV Treatment Update (HTU) asked Professor Joel Palefsky (JP) and Dr Paul Fox (PF) about how to prevent, diagnose and treat anal cancer.

HTU: **Let's start by talking about prevention. We know that a very high proportion of the population will have acquired at least one strain of HPV very soon after they first start having sex. We now have two preventative vaccines, one of which, *Gardasil*, is now being offered on the NHS to pubescent and adolescent girls, in order to try and prevent the future development of cervical cancer. Do we know enough yet about whether HIV-positive adults should consider the vaccine to prevent anal cancer?**

PF: There's almost certainly going to be no benefit whatsoever for someone in that category, because the chances of them not having already been exposed to all the different types of cancer-associated HPV strains are fairly remote. So they'll either have an ongoing infection or they'll already be immune to it.

JP: My own personal opinion is that we should not be offering the vaccine yet to sexually active adults, HIV-positive or not, until we have data showing that it works in the anal canal, and we also need to know that it's safe for HIV-positive people.

HTU: **Are there any ongoing studies in HIV-positive men and women?**

JP: There are two different studies currently enrolling adult HIV-positive women, one in India, and another mostly in the United States. And at UCSF we're now enrolling a study of HIV-positive men. The primary aim of all of these studies is to determine the vaccine's safety. We want to make sure that we're not causing CD4 counts to plummet or the HIV viral load to go spiralling out of control; we don't expect any of that to happen, but we have to show it. And we also want to see whether people are able to mount titres [sufficient HPV antibody levels]. Our experience of Hepatitis B vaccination suggests that the lower your CD4 level, the lower your response. However, we're optimistic that even people with low CD4 levels will respond well, but, again, we need to show that. So then the big question is – is it going to be of any clinical value? And that remains to be seen because the vaccine only works when you've not been exposed to a given HPV type.

HTU: **What are the latest data on the protective value of condoms for both men and women?**

JP: The data actually are not quite as hopeless as we used to think. One well-done study from the University of Washington showed that if women's partners used condoms 100% of the time, the women had a 70% reduction in acquiring new HPV strains. And we looked at HPV transmission among gay men in our Explore cohort and found fairly similar data: when the men reported that their partners used condoms for insertive anal intercourse all the time there was nearly a 70% reduction in the detection of new HPV infections. We tell people that we treat in our clinic to use condoms for the usual obvious reasons, but also to prevent infection with new HPV types.

HTU: **But if we've already been exposed to HPV – and your data suggest that almost everyone who is HIV-positive has been – is there any point in being concerned about further HPV acquisition in adults?**

JP: Everything we know about the biology of HPV infection is that the more strains you have, the worse it is. We work very hard to get rid of a high-grade lesion, which is usually due to one particular high risk HPV subtype, but if you then acquire another high-risk HPV subtype you could be starting the process all over again. So my reasoning for recommending condom use, and for pursuing adult vaccination, is the hope that, even if somebody's had multiple sexual partners, they will not have encountered all of the HPV types that the vaccine protects against. So while there may not be complete protection, there may be at least partial protection.

HTU: We know that gay men who practise anal sex are the people at the highest risk of multiple anal HPV infection. We also know that many women – especially HIV-positive women – also have anal HPV infection. But isn't it surprising that studies are also now finding that HIV-positive men who say they have never had anal sex also have anal HPV infection?

JP: Anal intercourse may be the most efficient way to get anal HPV, but it is by no means the only way. Another way is touching your sexual partner and then touching yourself. So the introduction of a finger or a toy around the opening of the anus may be enough. In the case of women there may be direct shedding from the cervix into the anus. There is also a possibility that men may also have penile [HPV] infection and they or they partner touches their penis and then their anus. So even if you've never had anal intercourse, just having had a finger near the anal canal can transmit the virus. So it's utterly unsurprising to me that people who say they've never had anal intercourse can still have HPV infection.

HTU: **So you think that all HIV-positive individuals should be screened for the full spectrum of anal HPV disease – from warts, to pre-cancer to cancer?**

JP: Yes. I think anybody who's HIV-positive should be screened regardless of gender or risk factor for HIV.

PF: I'm inclined to agree. But I don't think the NHS is going to buy into it, unfortunately, because we haven't had any large studies proving the benefit of screening. It's very difficult because, of course, what happened with cervical cancer is that screening and treatment happened before the evidence showed that it was really effective. And some people think that we should do the same with anal cancer. In an ideal world with limitless resources, then of course that's what we should be doing. But, of course, the reality is that the NHS is always going to look at everything from a cost-effectiveness viewpoint.

JP: It's true that people want to know, if they're going to spend this much money, if they're going to subject patients to this much discomfort, is there a clinical benefit? And if the definitive study to show that the screening and treating of high grade AIN will reduce anal cancer has not been done, there are excellent reasons to believe it will [do so] based on what we know about cervical cancer screening. However, that study still needs to be done and we're actually in the early planning stages of doing such a study. We want to get it done as quickly as possible, which means, from a study design stance, we'll have to enrol a very large number of people given the [relatively low] incidence of anal cancer. And so we're hoping to be able to monitor people for five years to get enough of a number to show a statistical difference if there is one.

PF: And at the Chelsea & Westminster we're about to invite the vast majority of patients into a three-year screening project to try and get a lot more information. We need to know if screening for, and treating AIN [anal pre-cancer], actually makes a difference. I think it's likely, otherwise I wouldn't be doing it, and so far, in our pilot programme, I've been able to pick up early cancers and get rid of them. If you pick these things up early you can just do local excision, you don't need to do the chemo and radiotherapy, which is a very good situation to be in.

***HTU*: If you do think there are benefits, and clinics in London and Edinburgh have had pilot screening programmes, shouldn't HIV clinics be trying to find ways to implement some kind of screening now, regardless of recommendations from national bodies? Or do we need more data, or perhaps, more importantly, more people with the right kind of expertise?**

JP: If you do decide to screen, I would strongly recommend you don't do that until you have an entire team in place. It's easy to do an anal Pap smear but you also need someone well skilled in high-resolution anoscopy, and surgical back-up, and pathology. If you have all those, then you're in business. But until you can offer patients good diagnostic approaches and good treatment approaches, then I think you're actually doing them a disservice.

PF: I see people from all over the UK. Apart from my colleague, Dr Nathan at the Homerton, after all these years of us both doing it, nobody else that we're aware of is actually doing high-resolution anoscopy. So it's not very brilliant for such a large country with so many HIV-positive patients, is it? Still, I think anal Pap smears are something that can be done pretty much anywhere and combined with self-examination or clinician observation, I think that's almost as good – possibly as good – as doing high-resolution anoscopy. Although anoscopy gives you a better quality of information, and it's always reassuring to be able to look at a lesion and to see what it's doing, I do wonder whether that's ever really going to be the best way forward. I wonder whether adopting the cervical cancer model is necessarily appropriate.

***HTU:* But do you think we currently have effective enough treatments to promote widespread screening?**

PF: Although our current treatments are all helpful, and you can get rid of individual lesions, none them are particularly fantastic.

JP: I think infrared coagulation (IRC) has really revolutionised treatment, and that's why I'm pushing forward with our randomised, controlled study now, because I think we have something that we can offer. We have about a 70% success rate in what I would consider to be the toughest population – HIV-positive men with widespread high-grade AIN.

PF: I think that the 70% success rate of IRC is perhaps slightly over-optimistic. What the 70% means is that if you treat a lesion with IRC and you look at it again three months later, in 70% of cases you will find that that lesion has gone. But there may well be a new lesion somewhere else and that lesion actually might reoccur a year or two later – we don't have the length of follow-up data to know. I see AIN lesions actually just disappearing and then reappearing again several years down the line. I do agree that it's a useful thing to do but I'm not

convinced that it is as helpful as it might be in the long term.

HTU: In the absence of screening programmes, what can HIV-positive people practically do? Are there any obvious signs of anal cancer?

JP: People who don't have the ability to enter a screening programme should have a regular digital rectal exam and also pay attention to certain symptoms, for example, anal pain. There may be many other causes, of course, such as a haemorrhoid, or a fissure [small tear], but if it's unexplained pain then I worry about cancer. I'd also look out for changes in anal bleeding. Many people have bleeding as part of their normal daily existence, but if it is something that's different, then something's changing, and I worry about that.

PF: The key to stopping people from dying of anal cancer is for them to be aware that they are at risk and to know how anal cancer manifests itself. Once a high-grade lesion starts turning into something a bit more sinister, they start to become palpable – you should be able to feel a hard lump. And since that's still at a pre-invasive stage, it is an opportunity to actually get something done. Anyone who is self-examining on a regular basis should not die of anal cancer because they should pick it up at a very early stage. I only see patients every six months, so I encourage them to regularly self-examine anyway because they might develop a lump a couple of weeks after I've seen them.

HTU: What's the difference between feeling a wart, for example, or even feeling the prostate, compared to feeling a lump that could be cancerous?

PF: First of all, the prostate is further in than you need to be; you only really need to feel a couple of centimetres, which is up to the first knuckle. And basically that's where the sphincter muscle is contracting. And that should feel pretty smooth. And if it doesn't, then someone should look at it with a proctoscope to see what's going on. Your HIV clinician or a sexual health clinic is probably the best place to go for that. Even if you do feel a lump, though, there's a good chance it's just going to be a wart, and cancer does not look like warts and warts don't look like cancer. But anyone with a lump of significant size should just go straight to a surgeon as a matter of urgency to have an excision biopsy. Of course there is the issue of how long it then takes to actually get it looked at by someone who really knows what they're doing, and there's certainly a role for regional anoscopy clinics to deal with those kind of issues.

HTU: Even though we haven't got enough answers for routine screening, it seems that there are things we can do now to save lives. What else can we to push the agenda along

JP: I think where we are with anal cancer is very analogous to what happened in the early days of the HIV epidemic. It was only the advocacy of HIV-positive people that really pushed the agenda forward.

PF: Unfortunately, there's still a lot of late detection and late presentation of anal cancer because HIV-positive patients are either not aware or they just don't want to think about it. I mean it's surprising how many HIV-positive gay men just really don't want to think about putting a finger 'up there', for instance. It's partly out of fear, isn't it? They're just frightened of what they might find, so they just don't want to do it. But studies are finally going to happen and it is an exciting time. It's going to take a few more years before we know what's best and what we recommend. I mean it would be an awful shame to spend millions of pounds and upset a lot of chaps and worry them all perhaps unnecessarily only to find that actually just sticking their finger up their bottom, you know, once a fortnight or something, is as effective as having high-resolution anoscopy.