nam
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hiv treatment update

Gus Cairns

in this issue

In *Scattered Pictures* on page 8, we speculate that "for many [people with HIV] the biggest concern may be whether we are more likely to develop memory loss and dementia".

What, really? Bigger than worrying about heart disease or stigma or the recession? Well, yes, if the reaction from members of our readers' panel and others to draft versions of the article was anything to go by. "Please don't tell me this is true," was the general tone of some responses.

So it's important to emphasise that what the piece uncovers – that over half of people with HIV performed worse than the general population in a battery of tests on memory and thinking – is not as frightening as it sounds.

Firstly, the differences observed would, in the majority of cases, be unnoticeable in daily life. Secondly, the same studies found that nearly as many people recovered from impairments of co-ordination and concentration as acquired them between tests. Thirdly, it found that HIV-negative people in the same risk groups – for instance, gay men – also had an unexpectedly poor performance. This implies that behavioural factors (such as the amount of ecstasy you've taken in your life) or social ones (such as whether you've experienced bullying and therefore have difficulty in stressful situations like tests) may be operating here.

Research from the last few years suggests that HIV infection, especially if at any time you've had a low CD4 count, continues to exert an influence a long time after CD4 counts go back up. With HIV, your guts are (on average) a little more sensitive; your lungs are a bit more prone to cancer; your blood vessels a bit more likely to fur up. It follows that this picture applies to the brain too.

This implies we should treat it well, like any other organ: give it plenty of sleep, a good diet, exercise – both physical and mental, and try not to poison it with alcohol and other toxins, and it will serve us well into a sharp old age.

The fear of brain impairment is also the fear of stigma, of course, too. Mental and neurological illnesses are probably two of the few remaining areas of health where we sometimes turn our heads away or blame the victims. Cancer used to be stigmatised in the same way a generation ago. But a number of accounts of what it's like to have the illness, including the recent and very public death of reality TV star Jade Goody, have helped to raise awareness of the issue. Death from cervical cancer is especially tragic as it's an almost entirely preventable disease. See page 4 for more on what women with HIV can do about it.

Lastly, we write this piece during a period of glorious spring sunshine. What better time to get on your bike or go for a run round the park? In order to encourage people to join our team for the Crusaid Walk for Life on Sunday 7 June we've listed the numerous benefits of exercise on page 3. Bringing us back neatly to mental health, one study found that people who took exercise were four times less likely to get stressed than couch potatoes. Think of that, put on your running shoes, and come and join us in London. Soon all your cares will melt away and you will be doing it for a good cause too.

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upfront

Why fit is happy: exercise, mood and HIV

The team here at NAM will be taking part in a couple of fundraising events involving exercise this summer. At the less demanding end of the scale, a number of us (14 so far) will be joining the annual Crusaid Walk for Life on 7 June: see www.walkforlife.co.uk and search for NAM. This ten-kilometre stroll raises thousands of pounds every year for HIV charities. We would love you to join our team and get sponsored, have fun and help us raise vital funds for NAM. Of course if you can't make the day, we still need your support! Please sponsor us using the enclosed form or at www.walkforlife.co.uk.

Passing us in the fast lane, some of the fitter members of the team will be participating in the London Triathlon on 1 and 2 August. Watch this space for more information.

Exercise, it's been said, is so good for the body and mind that if it were a pill, pharmaceutical companies would be fighting to patent it. That may seem obvious: of course being fit should mean you get fewer illnesses. But what are the specific benefits for people with HIV?

In the post-HAART era there has been little research on the effects of exercise on HIV infection itself. The best data we have are from 1991, when a study[1] found that an exercise programme produced a significant CD4 count increase of about 50 cells/mm^3.

Even very moderate exercise boosts the immune system compared with doing nothing. Researchers[2] measured immune function in 15 women when they had taken a 30-minute walk and when they had spent the 30 minutes sitting and found increases in many different parts of the immune system after exercise.

However, there is also evidence that too much intense exercise can reduce immunity. More than 90 minutes of high-intensity exercise can make athletes susceptible to illness for up to 72 hours. This is important information for those who compete in longer events such as marathons. The reason appears to be that very high-intensity exercise increases the stress hormone cortisol, which suppresses the immune response.

More recently, studies of exercise have concentrated on improvements in fat distribution, body shape and cardiovascular health measures like cholesterol. Exercise regimens have tended to produce consistent, but relatively small, decreases in fat accumulation inside the abdomen, significant decreases in total cholesterol, reductions in insulin resistance (the precursor of diabetes)[3] and lowering of blood pressure[4] and triglycerides, other heart disease indicators.[5]

Studies of resistance[6] and aerobic exercise[7] have found significant increases in cardiovascular fitness and mood. Exercise may also have more psychological benefits than previously thought. Even 30 minutes of exercise has been shown to improve the mood of depressed patients[8] and just six 20-minute sessions of aerobic exercise significantly reduced the tendency of study participants to get anxious when exposed to stress.[9]

Aerobic exercise means exercise that gets your heart beating faster such as running, cycling, swimming, even dancing. A good level to aim for is 20 minutes three to four times a week.

Resistance exercise builds muscle (you don't have to use weights: sit-ups and press-ups are resistance exercises). Aim for about 40 minutes, one to three times a week. Exercise all muscle groups and do an aerobic warm-up first.

For more information, look up 'exercise' on www.namlife.org.

Finally, don't start any regime without consulting your doctor and, especially with weight training, get instruction in how to do it safely. Londoners could start at the YMCA's 'Positive Health' – see www.ymcaclub.co.uk or phone 020 7343 1700. They can also tell you about schemes elsewhere in the UK.

The highs and lows of an HIV-positive marathon runner

Jim Pickett is Director of Advocacy for the AIDS Foundation of Chicago (AFC). The AFC offer volunteers free marathon-running training in return for the sponsorship they raise.

"I was a big fella eight years ago and decided I had to get fitter. I started running but frankly looked on marathon runners with a mix of pity and scorn: why would anyone put themselves through that?

"However, the training deal came up and I went for it. I found I loved it – it's really hard but I've found strength and ability in myself I never knew I had. It's as much a mental exercise as physical. I did three marathons in Chicago and one in Florence."

The last one was not such a good experience, however. "We did it in 90-degree heat and they hadn't provided enough water. It was called off when I was at the 16-mile mark because people were collapsing.

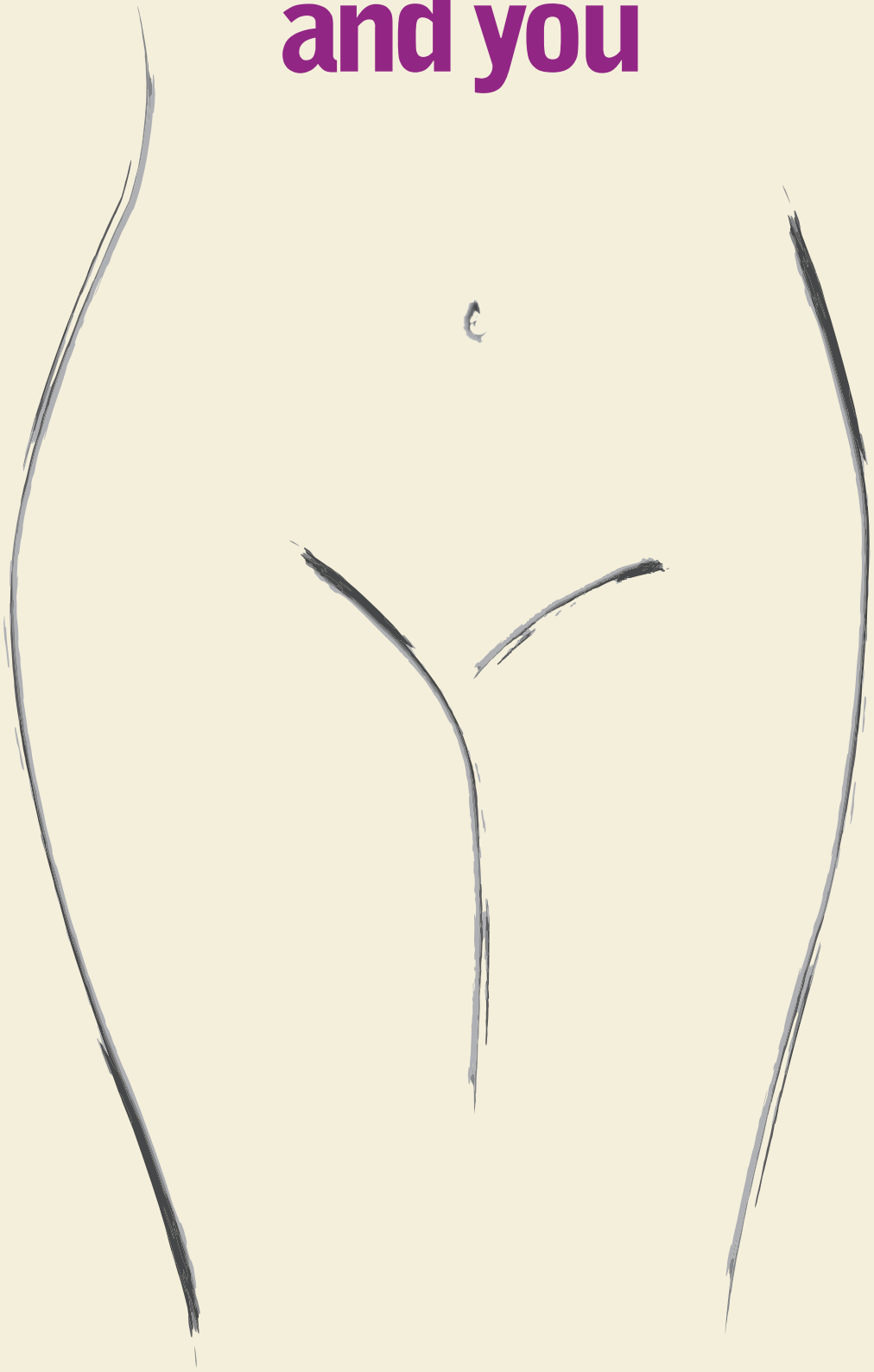
"Since then I worry I've become a bit of a potato and want to start again, possibly do a half marathon.

"My recommendation if you want to do any kind of exercise is: be kind to yourself. If you run, do it somewhere nice. If you like music, take your iPod.

"Make it do-able. If it's a two-mile walk then do that. Start doing little runs during the walk, that sort of thing. Anyone can do it, especially if you do it with friends for support."

Crusaid
walk for life
walk for nam

cervical cancer and you



The recent death of reality TV star Jade Goody has created a huge upsurge of concern about cervical cancer, and getting screened for it. HIV-positive women are especially likely to benefit from early and regular testing and treatment, reports *Gus Cairns*.

Cervical cancer is the second most common type of cancer in women worldwide, and the most common cause of cancer-related deaths in the developing world.[1] If you develop invasive cervical cancer you have a less than 50% chance of survival.[2]

But Jade Goody was unlucky to die from it. Cervical cancer is rare in women of her age and she may have had a less common variant of it. There are fewer than 30 deaths a year due to cervical cancer in women under 25 in the UK.

Over a lifetime, though, about one in 117 women will develop cervical cancer in the UK.[3] But survival rates are continuing to improve: about two-thirds of women in England and Wales who develop cervical cancer will live for more than ten years after diagnosis.[4]

Most deaths from cervical cancer are preventable. The NHS calculates that if overall coverage of 80% were achieved with their cervical screening programme, there would be an eventual 95% reduction in cervical cancer deaths.[5]

One group of women who might particularly benefit from having more frequent cervical screening is women with HIV. HIV-positive women are twice as likely to be infected with HPV, the virus that causes cervical cancer, than HIV-negative women (see box). They're three to four times as likely to develop pre-cancerous cells if they are. And they are about twelve times as likely to develop invasive cervical cancer unless, in a simple procedure under local anaesthetic, these cells are removed.

The risks for HIV-positive women

Because a weak immune system controls HPV less well, women with HIV are at a disadvantage when it comes to rates of infection, the persistence of infection, and progression (the development or worsening of HPV-related conditions) and so need earlier and more frequent monitoring and earlier intervention.

Whereas only 15% of HIV-negative women may have current HPV infection, a large study in the USA found that nearly 60% of HIV-positive women were currently infected with at least one type of HPV.[6]

We did a survey which showed that about two-thirds of our HIV-positive patients were aware they needed an annual screen, but that only half of them had actually had a screen in the last year.
Dr Fiona Boag, Chelsea and Westminster Hospital.

A study in pre-antiretroviral therapy (ART) days[7] called the Women's Interagency Health Study (WIHS) looked at a group of HIV-positive and negative women. It found that one in 25 HIV-negative women a year acquired new HPV infections but that the rate was 80% greater in women with HIV and three times greater in women with CD4 counts under 200 cells/mm^3. Once they were infected, women with HIV with a high viral load were 50% more likely to develop SIL, or to develop high-grade SIL if they already had SIL (see **glossary**). On the other hand, there was no statistical difference in the study between HIV-negative women and HIV-positive women with *high* CD4 counts and *low* viral loads.

So does taking ART in itself reduce HPV infections and cervical cancer? Here the evidence is mixed: women on ART seem to clear more HPV infections but some surveys have shown no reduction in rates of SIL and CIN (see **glossary**). This is probably because more women are living long enough now to develop persistent HPV infection; previously, many were dying of AIDS before they could develop it.

Screening and testing

Screening and treatment for pre-cancerous cells is a particular priority for women with HIV, since SIL can develop so much faster.

What causes cervical cancer?

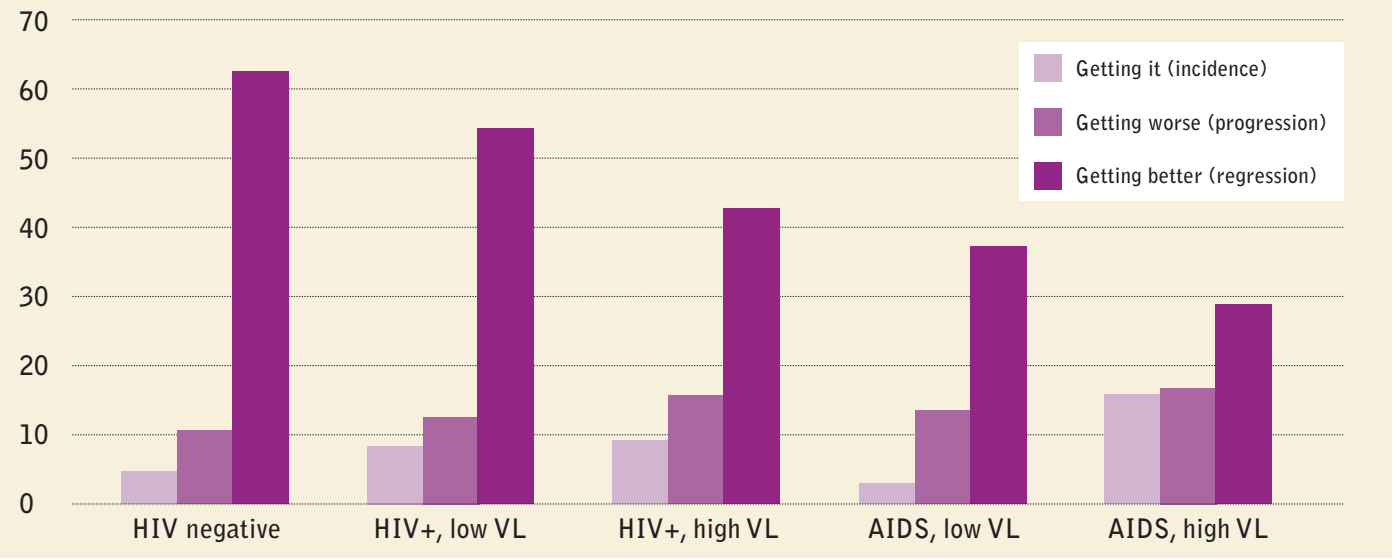
Cervical cancer is caused almost entirely by an infection – that of the human papilloma virus, HPV. HPV also causes a probable 90% of anal cancer cases and a minority of cases of cancer of the vagina, penis, and mouth. Only a small minority of people infected by HPV will develop cancer.

HPV is a whole family of viruses and there are about 100 different species, but just two types, HPV-16 and HPV-18, cause at least two-thirds of all cases of the most common type of cervical cancer. This is because they persist for longer and because they have acquired the ability to inactivate cancer-suppressing proteins normally produced by cells. For this reason the two highly effective vaccines developed in recent years, *Cervarix* and *Gardasil*, protect against these two types (*Gardasil* also protects against the two most common types that cause non-cancerous genital warts).

HPV is an extremely common infection. Three-quarters of HIV-negative women will catch at least one variety of HPV in their lifetime and half of them within two years of starting sex. However only 10 to 20% have a current infection and unless you have compromised immunity the body eventually gets rid of most HPV infections.

"It takes anything from a few weeks to 18 months for the body to produce antibodies (neutralising proteins) to HPV," says Margaret Stanley, Professor of Epithelial Biology at Cambridge University. "Once this happens the immune response gets rid of the infection in 80 to 90% of cases. It's the women who have persistent infection who are the ones at risk of developing cancer."

Women's Interagency Health Study: HPV infections and progression/regression after one suspicious smear test, 1994-99



In the USA the Centers for Disease Control has recommended that HIV-positive women should be given a smear test as soon as they are diagnosed with HIV and then six months later, and every year after that if test results are normal.

Given, however, that a possibly much higher proportion of women with HIV who have high-risk HPV types will progress to SIL and CIN, monitoring such as HPV DNA testing is being considered.[8] This is a viral load-type test that can detect any current HPV infection, not just ones that produce symptoms, and can determine what type of HPV is present.

In the UK, the British HIV Association (BHIVA) sexual health guidelines (published 2008) recommend an initial smear test and colposcopy at HIV diagnosis followed by a smear test every year.[9] They add that "CIN should be aggressively screened for and treated". They do not recommend HPV DNA testing.

Dr Fiona Boag of the Kobler Clinic at the Chelsea and Westminster Hospital in London says that there is confusion in the minds of both patients and clinics about how often to screen HIV-positive women and who should do it.

"Women will be screened on HIV diagnosis but clinics are only now getting round to offering annual screening, and the uptake isn't as good as it should be. We did a survey[10] which showed that about two-thirds of our HIV-positive female patients were aware they needed an annual screen, but that only half of them had actually had a screen in the last year."

"Patients get confused because they also get letters from their GPs for three-yearly screening, as well as from us," she adds.

In England the NHS took the controversial decision in 2005 only to offer screening to women over 25, but Boag confirms that HIV-positive women under 25 are also offered annual screening, "though some clinics still aren't aware of the BHIVA guidelines". So it may be necessary to be proactive to make sure you get your annual screening test.

The screening test for cervical abnormalities involves inserting a small spatula into the vagina and brushing a sample of cells from the cervix. This is often still called a 'smear' even though doctors now use a technique called liquid-based cytology (LBC) that involves putting the sample in a bottle rather than onto a microscope slide.

The test looks for abnormal cells that have been 'excited' by HPV. This is so-called SIL (see **glossary**). If this is detected, a **colposcopy** will be ordered; this involves a doctor making a visual examination of the cervix (while the woman is in stirrups) with a binocular microscope. What they will be looking for is cervical intraepithelial neoplasia (CIN) – see **glossary**.

If it is left unchecked, then the CIN *may* develop firstly into a localised 'pre-cancer' called CIS (carcinoma in situ, see **glossary**), which can still be operated on locally, and then into invasive cervical cancer needing radical treatment.

It's important to emphasise that even if you develop CIN, malignant cervical cancer is not an inevitability. "If I knew why some women develop cancer and others don't, I'd be on the plane to Stockholm to get my Nobel Prize," says Margaret Stanley. Although about one in six women with HIV and HPV have either LSIL or HSIL (compared with one in 20 HIV-negative women), only about one in 400 HIV-positive women (0.24%) would develop invasive cervical cancer, which can take ten to 15 years to develop, if not treated.

Symptoms and treatment

CIN and cervical pre-cancer are more often than not asymptomatic, but if CIN is not detected it can produce symptoms. The most frequent one is bleeding between periods or after sex, or at any time if you are post-menopausal. Other symptoms include a smelly vaginal discharge, pain during sex and pain in the pelvic area in general.

Treatment involves a variety of methods according to the stage reached. If you have SIL, and possibly CIN stage one, there may be no treatment advised other than follow-up tests, though you may be more likely to be offered treatment if you have HIV. Treatment for CIN may involve removal of the cells by non-surgical means such as **cryotherapy** (freezing with liquid nitrogen) or **laser ablation** (burning off the cells with a laser). Laser treatment is somewhat more effective and more usually offered. This treatment is usually done using local anaesthetic on an outpatient basis.

Simple surgical techniques include **loop excision**. This involves the removal of a layer of pre-cancerous cells with a 'laser knife', while **cone biopsy** involves the laser removal of a deeper layer of cells. These are minor day-surgery procedures. They are usually done using local anaesthetic though a general may be needed.

You may feel some discomfort during these procedures but they should not be painful after the initial local anaesthetic injection, though you may experience period-like pain and feel generally unwell for a few hours afterwards. There may also be some discharge or bleeding for a few days. Women are advised not to have sex, nor to use tampons, for four weeks after these procedures to allow the cervix to heal.

Studies have found that CIN is more likely to reappear in women with HIV than in HIV-negative women: one study[11] found there was an 8.6% chance of high-grade CIN reappearing within a year. This was associated with low CD4 counts and not taking HIV treatment and also with incomplete removal of cells. The BHIVA cancer guidelines[12] therefore recommend that doctors should err on the side of caution and use procedures that will ensure all cancerous cells are gone.

For persistent high-grade CIN and CIS, hysterectomy (removal of the womb) may be the treatment of choice. With more invasive cancers, this may have to be supplemented by radiotherapy, chemotherapy and possibly other surgery.

The vaccine

Finally, is it worthwhile getting vaccinated against HPV? After the success of the trials of the HPV vaccines, which prevented 95 to 100% of infection[13] the UK, like many other countries, has recommended that either *Gardasil* or *Cervarix* be given to all adolescent girls; in the UK this means those aged 12 to 14.

It has been assumed that getting the vaccine if you are HIV-positive is a waste of time, as so many women with HIV already have HPV, and are much more likely to be infected with multiple types than HIV-negative women.[14] However even in HIV-positive women the body's own antibody response may eventually get rid of those infections. Is it worth getting the vaccine in those circumstances?

Margaret Stanley thinks it is. "If I was positive I might well think about seeing which types of HPV I had and if I *didn't* have types 16 or 18, getting the vaccine." There is also evidence that the vaccines prevent infections by a quarter to a third of other high-risk HPV subtypes.[15]

At present you would have to get the HPV vaccine privately – where it costs in the region of £420 for the three-jab course. Nonetheless, some women are coming forward for it. Dr José González-García of the private sexual health clinic Freedom Health told *HTU* that there had been a 20% rise in women coming forward for HPV check-ups and cervical screening, both in his private and NHS work. The vaccine, however, will only protect the women who do not currently have HPV types 16 and 18.

Recommendations

The main recommendations for positive women are therefore:

- have a screening test on diagnosis, six months later and then at least once a year, and don't wait for the clinic to send you reminders
- make sure you get the results (no news isn't necessarily good news) and take up any follow-up screening or treatment to have any suspect cells removed promptly
- urge your clinic to provide an HPV DNA test to see what types of HPV you have. If you don't have types 16 or 18, consider the vaccine.

If you do all these things, you have little risk of getting an almost entirely preventable disease and increase your chances of living to the ripe old age that Jade never had the chance to see. ■

Glossary

Cervix the neck of the womb, a tight 'collar' of tissue that closes off the womb except during childbirth. Cancerous changes are most likely in the transformation zone where the vaginal epithelium (lining) and the lining of the womb meet.

ASCUS (atypical squamous cells of undetermined significance) This indicates that a screening test has found cells that are mildly abnormal but that the cause of the abnormality is unknown. If ASCUS is detected doctors will probably order a repeat test.

SIL (squamous intraepithelial lesion) This term is used to describe the detection of abnormal cells that have been 'transformed' by HPV into a possibly pre-cancerous state. According to the degree of cell change this will be called low-grade or high-grade SIL (LSIL or HSIL). If SIL is detected a colposcopy (see main piece) will usually be ordered.

CIN (cervical intraepithelial neoplasia) This means changes to the cervical tissue which can be seen on visual examination through a colposcope. These are graded CIN1 to 3 according to whether one-third, two-thirds or all of the normal cells within the affected area are replaced by pre-cancerous ones. CIN1 is often left untreated; higher-grade lesions will probably need removing.

CIS (carcinoma in situ) This is often referred to as 'pre-cancer'; the cells have developed into cancer cells but have not yet become malignant, i.e. invasive, and remain restricted to the cervix. The chance of CIS turning into ICC (see below) are high and doctors will therefore make as complete as possible a removal of the affected cells.

ICC (invasive cervical cancer) This indicates that the cells have become malignant and acquired the ability to invade other tissues. More radical surgery (such as hysterectomy – removal of the womb), radiotherapy and chemotherapy may be needed at this point.

scattered pictures
brain impairment and HIV

Gus Cairns and *Theo Smart* investigate HIV-related brain impairment, memory loss and dementia

As people with HIV survive into old age there is increasing focus on conditions associated with ageing. The evidence that HIV increases the chance of developing things like heart disease and some cancers may cause anxiety, but for many the biggest concern may be whether we are more likely to develop memory loss and dementia. So it was not surprising that a group of studies on brain impairment presented at the Conference on Retroviruses and Opportunistic Infections (CROI) this year raised considerable concern amongst the HIV-positive community.

In the 1980s, obvious dementia was fairly common in advanced HIV disease, but became unusual after the introduction of AZT. Mild to moderate neurological disorders continued to be observed in people with late-stage AIDS,[1] but there was clear evidence of improvement with the introduction of antiretroviral therapy (ART).[2] More subtle neurological symptoms seemed to persist in some people, though, despite the life-saving therapies that were so effectively managing other HIV-related conditions.

So in 2002, the US National Institutes of Health launched a multi-site study called CHARTER (it stands for CNS [central nervous system] HIV Anti-Retroviral Therapy Effects Research). It is looking comprehensively at the prevalence in people with HIV of neurological disorders – nerve or brain damage that can be detected by physical tests – and cognitive disorders – disorders in thinking and memory that can be picked up in psychological tests. It is trying to find ways of predicting whether people will develop brain impairment and diagnosing it accurately when they do.

To some people, CHARTER's first results were a shock.[3] It found that at study entry, out of the 1555 people with HIV in the United States whose brain function was measured, more than half – 53% – had some form of neuro-cognitive impairment. One in ten had clearly noticeable impairment, and one in fifty moderate HIV-associated dementia, though the prevalence of classic 'AIDS dementia' was under 1%.

So does this mean that more than half of us are already on the way to losing our minds? No. The evidence that HIV infection does cause a specific kind of mild impairment in mental function is strong, but it may not resemble or have the same causes as classic dementia, will not necessarily progress, and may not be noticeable in daily life.

Dr Simon Rackstraw is Medical Director of Mildmay UK, a hospital in Shoreditch, east London, which is the UK's only specialist unit for people with HIV-related brain impairment.

"CHARTER's findings are robust," he says, "however I'm not sure how important this mild impairment is."

Rackstraw continues. "Sensitive psychological tests can pick it up, but in real-life terms it's not interfering with daily life and people won't be noticing symptoms. You're talking about the sort of things – lack of concentration, losing things, clumsiness, forgetting names – that most of us experience at some time or other. The effects these tests pick up are the same sort of things that could be produced by a hangover, not enough sleep, or depression.

"The 10% with moderate impairment, however, may notice difficulty with relatively complex tasks like driving. Other people may notice changes better than the person concerned. "

Rackstraw explains that HIV-related brain impairment often presents a different picture from classic dementia. "People have difficulties with executive function – the ability to make choices and decisions – and may put things off more. Muscular co-ordination may be lost too. On the other hand verbal fluency is usually retained; people remain mobile and energetic, but get a bit chaotic. One of my patients talks very convincingly about running a share portfolio – though I'm not sure how effectively – but can't open a can of baked beans. Classic Alzheimer's is more memory-oriented and people become more apathetic."

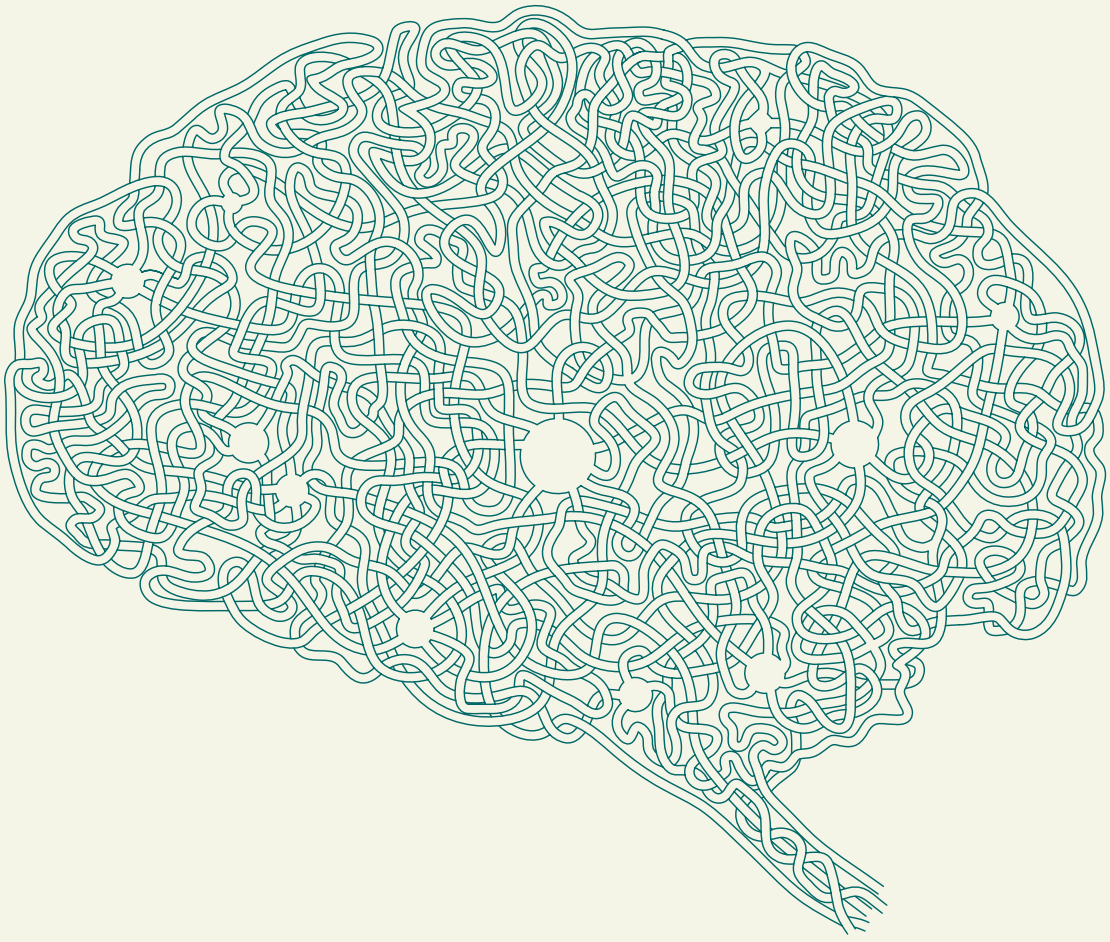
Very importantly, and of some reassurance to those of us who keep losing their keys, mild brain impairment appears to be reversible. In another study presented at CROI, Dr Scott Letendre[4] cited the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT), a study of 1160 HIV-positive people who had been on HIV treatment for an average of about 20 weeks.[5] At the start, despite most people being on treatment, about 39% demonstrated at least mild impairment. When ALLRT re-tested participants 48 weeks later, it found that over half of people who had impairment at baseline still had it, but in 44% of cases the impairment had apparently reversed – brain function appeared normal again. However, among people who had normal results at their first testing and then were re-tested, just over a fifth (21%) had new impairment.

You're talking about the sort of things – lack of concentration, losing things, clumsiness, forgetting names – that most of us experience at some time or other. The effects these tests pick up are the same sort of things that could be produced by a hangover, not enough sleep, or depression.
Dr Simon Rackstraw of Mildmay Hospital, on tests showing that more than half of people with HIV had impaired brain function.

In other words HIV brain impairment appears to be *on average* progressive amongst this group, but slowly, at a rate of about 4% more patients with some degree of brain impairment a year. But the average conceals the fact that nearly half of patients who have brain impairment at one test don't have it next time.

Even then, it isn't clear that HIV-related neurological impairment will progress to HIV-associated dementia if left untreated, or even that they're the same thing: there may be more than one pathological process involved in the development of neurological problems in people with HIV.

In addition, although age is a factor, some recent studies showed that HIV-specific brain impairment is by no means restricted to older people. One study from St Mary's Hospital in west London,[6]



found that – relative to others of their age – HIV-related brain impairment was actually more common in *younger* people with recent diagnosis. Rackstraw confirms this. "The youngest I have currently on the ward is 22," he says, "and I've treated a number of teenagers." HIV brain impairment and age may not always be linked.

What causes it?

What are the risk factors for brain impairment, and why might some of it reverse? The CHARTER researchers found that the strongest predictor of brain impairment was the lowest-ever CD4 count (the CD4 nadir) – though having a high current viral load was also important. One more reason to start HIV treatment early.

Simon Rackstraw comments that, "I have seen remarkable recoveries just from putting people on antiretrovirals. Over 90% of our referrals are either people diagnosed late or people who dropped out of medical care. If we see brain impairment progressing in people on antiretrovirals, it's due to a cause other than HIV like alcohol abuse."

HIV disease is not the only cause of brain impairment. Hepatitis C has neurocognitive effects of its own. Alcohol and substance abuse, stress and poor sleep may all be more damaging than HIV itself. Then there are psychological disorders like depression. "Depression may look like brain impairment," says Rackstraw. "We find that sometimes if patients are given antidepressants this is sufficient to produce a remarkable recovery." In other words, there are modifiable factors which, when changed, may improve function.

Being in an HIV risk group may raise your risk of brain impairment in itself. Two pre-ART studies, found rates of 17 and 9% of neurocognitive impairment in a control group of HIV-negative gay men where the expected rate in the general population is about 3 to 4%.[7,8] It's not known why.

HIV in the brain

What might HIV be doing to the brain? It doesn't replicate in nerve cells, so one theory was that damage occurred because HIV, brought inside immune-system cells, was setting up an inflammation in the brain. It's not clear, however, that there's a strong association between current HIV viral load in the blood and viral load in the cerebro-spinal fluid (CSF, the fluid that bathes the brain and spinal cord), or between CSF viral load and dementia.

Instead, the reason brain impairment may get worse despite HIV treatment and with an undetectable viral load is because early HIV infection may set up brain cells to be permanently more vulnerable to the conventional risk factors for brain impairment (alcohol, depression, drugs and so on). "This means that even if you take the HIV out, it may not stop," comments Simon Rackstraw. We may need to take care of our brains better than other people.

Because neurocognitive problems have so many different causes, a team from St Thomas' Hospital in south London recently conducted a smaller study[9] amongst HIV patients on ART with few other risk factors to try and see if brain impairment was more common even amongst them than the general population.

They selected 40 gay men who had been on stable HIV therapy for over six months. They had minimal recent and lifetime use of alcohol, cannabis and other recreational drugs, had no hepatitis B or C, and no current or past significant psychiatric, medical or neurological conditions. They identified 20 men aged 20 to 40, and 20 men aged 50 to 75, for the study and put them through a large battery of neuropsychological tests. They also put two control groups of 20 HIV-negative gay men with similar characteristics and ages through the same tests.

There was a tendency for the HIV-positive men in both age groups to have more cognitive impairment but this did not reach statistical significance. Fifteen per cent of HIV-positive men had brain impairment compared with 10% of the older HIV-negative men and 9% of the younger ones. Note that even in the HIV-negative men, there was three times as much brain impairment as expected in men of their age.

The brain images revealed a specific and significant loss of grey matter (the nerve cells that actually do the thinking) from a part of the brain called the medial and superior frontal gyrus. This area, located right above the centre of the forehead, deals with decision-making and choice. However, the patients with loss of nerve cells were not the same people as the patients who had cognitive impairment.

HTU talked to HIV consultant Dr Babu Kulasegaram and neuropsychiatrists Dr Mervi Pitkanen and Professor Mike Kopelman about their study.

"I was seeing more and more patients who were coming in and saying 'I'm not as sharp as I was'," says Kulasegaram. "So we wanted to see if there was any sign of brain impairment in people on HIV treatment with every other causative factor eliminated, as far as possible." One possibly controversial decision was only to include white British gay men. Why exclude other ethnicities? "We very much want to look at the African population too," says Pitkanen, "but some of the neurocognitive tests are very culturally specific and we wanted as homogeneous a group as possible."

HIV treatment and brain impairment

Are some HIV drugs better than others for brain impairment? In the large US studies, having a detectable CSF viral load and performing less well on tests was associated with using antiretroviral drugs less likely to get into the brain.

"We don't have to put every HIV patient on brain-penetrating regimens," says Simon Rackstraw, "but I've put people with impairment on drugs that get into the brain better and they have improved."

At St Thomas', Mervi Pitkanen comments that although people with HIV may be more vulnerable to brain impairment there is no indication that, if their risk factors are controlled, it will inevitably get worse.

"Our brain scan images may be picking up on trouble to come," she says. "But we know we can say to diabetics: '*If* we keep your diabetes under control, there's a pretty good chance we can avoid you getting kidney problems 20 years hence.' We need to be able to offer the same reassurance to people with mild brain impairment – that if we keep it stable, it won't lead to dementia."

The best thing to do, then, is to try to eliminate as many of those other risk factors as possible – cut down on alcohol, recreational drugs and smoking, treat high cholesterol and blood pressure, and get help tackling depression. The brain is a very adaptable organ and can, up to a point, compensate for losses of nerve cells and connections. Numerous studies in HIV-negative people have found that the more active you keep your mind as you age, the less likely you are to develop dementia. In one study[10] researchers found that reading, doing puzzles, playing board games, playing musical instruments, and dancing were associated with a reduced risk of dementia. Your daily Sudoku really may help to keep your mind sharp.

What if it does progress, however? Even if people with HIV only get as much dementia as everyone else, we may still need HIV-specific support and housing. "There's a real lack of supportive housing schemes and care homes for people with brain impairment and HIV," says Simon Rackstraw. "We still get supportive housing schemes saying things like 'We would take this person but they have HIV'. Conversely, by no means all our cognitively impaired patients are old and a typical nursing home is no place for them. Unfortunately the cognitively impaired don't write to their MPs."

Although we should look to the future with optimism, we need to be realistic too. Who knows what it will hold? ■

Living with brain impairment: Lee's story

Lee, a 52-year-old gay south Londoner, was diagnosed with HIV at his workplace: he is a former healthcare assistant. He'd run a lot of risks in his 20s, but put off testing for HIV till he came down with bacterial pneumonia in 1997. "I didn't want to know: HIV felt like a time bomb waiting to go off."

When a colleague finally persuaded him to have an HIV test he found he was lucky to be alive: his CD4 count in that first year hovered between zero and five.

Distressed at the death of his partner, he took an overdose of his HIV medications in 1998. Lee blames the brain impairment and mental problems he's suffered from since then on this. Whether it was the cause or a symptom of them, he's since survived other life-threatening nervous system illnesses, a section under the Mental Health Act, two stays in conventional psychiatric hospitals, and a number of shorter and longer rehabilitation stays at the Mildmay.

"It was really weird after I took the overdose. I was having nightmares when I was awake."

He was moved to the psychiatric ward at the Royal Free Hospital. "That was a low point. I remember crying and thinking 'Get me out of here'. I'd heard of the Mildmay and eventually they visited and assessed me for rehabilitation. They did a good job – got my CD4s up to 90. I enjoyed it there: we were allowed to go out, though they send the nurses out to watch you and assess how you're doing. If you feel ready to leave, they do a big meeting with doctors, nurses, a social worker and an independent doctor. It took me three goes to get out."

The brain impairment has intermittent, and selective, effects, he explains. He has great difficulty remembering the sequence of events and how long his stays in hospital were. On the other hand he is currently briefing a solicitor in order to reverse the local council's refusal to extend the tenancy of his flat to his current partner.

How does he assess his own state? "I know I'm getting bad when I start shaking and [feeling] stressed. I feel myself getting aggressive and having suicidal thoughts. These days I've got ways of stopping it happening before it goes too far."

As for getting better, he says, his yardstick is phone numbers. "At the Royal Free, every phone number I'd ever remembered went out of my head. Then one night at the Mildmay my brother's popped into my head and I rang him. The others all reappeared slowly."

He's had a couple of other episodes of neurological illness. One may have been partly self-inflicted. "I came off my HIV pills in 2005. It was an experiment; I wanted to see if it worked." His CD4 count stayed stable for quite a while, "but eventually my weight dropped down to seven stone."

He tells a funny and painful story. "I looked in the mirror and thought 'I look like I've got AIDS. I know, I'll piss off to Sitges!'" [the gay resort town in Spain]. Lee describes a scene where, staggering and hallucinating, he was arrested by three policemen at Gatwick. "I can't stop my mouth when I'm like that. I told one, 'I recognise you, I had you in a back room in Brighton'. Well, they didn't like that! They put me on a mental health section [compulsory admission] for six months in The Lambeth Hospital in Clapham. No one knew where I was.

"Eventually my niece found me. She alerted the Mildmay who got the mental health section reversed. The Mildmay had me in for months, got my CD4 count up to 255, highest it's ever been.

"I owe everything to the Mildmay, they keep getting me out of scrapes. I really wanted to go with my boyfriend when he died, but now, well, I don't want to get old and decrepit, but if I look like I do now at 60, I might not shoot myself! I want to get better still."

news in brief

Superinfection

HIV superinfection can cause illness and viral load spikes

People can catch a second HIV infection on top of their initial one – so-called superinfection – but what is less clear is how common it is and what the clinical consequences are. Researchers from London's Royal Free and Royal London Hospitals have now found that it may be relatively common in people not on treatment and may be accompanied by sudden rises in viral load. In some cases it may cause significant illness.[1]

Researchers selected gay male patients not on treatment who were having unprotected sex and had an unexpected rise in their viral load. In this pilot study eight patients were referred, and the patients' current HIV genetic sequences were compared with those in blood samples taken immediately after diagnosis.

Two out of the eight patients had viruses in their blood that were completely different from the one they started with. In one person superinfection was signalled, three years after diagnosis, by a temporary but very large increase in viral load, from about 3000 to over a million. The patient's HIV also changed from a drug-resistant to a non-resistant strain. However he did not experience any symptoms and he maintained a high CD4 count.

In the other case, however, five months after his initial HIV infection, the patient experienced a return of the symptoms he had experienced during his first infection: a flu-like illness with a headache so severe he was admitted to hospital with suspected meningitis. The HIV strain in his earlier blood sample was not drug-resistant but the one in the second sample was. His viral load, which had been 40,000, increased to nearly one million and his CD4 count fell temporarily from 430 to 240.

Lead researcher Dr Anna Maria Geretti told *HTU* that it was impossible to tell from this pilot study how common superinfection was because doctors only referred selected patients to this study. "But overall," she said, "a sudden increase in viral load of more than 0.5 log [a threefold increase] is seen in about 20% of untreated patients, compared with the usual more gradual increase over time." She added that the study suggested that patients who continue to have unsafe sex might be advised to start treatment early.

South Africa

HIV harmony in South Africa

Last month's South African AIDS Conference was marked by a more positive relationship between HIV activists and the South African government than existed during the presidency of Thabo Mbeki, *Theo Smart* reports from Durban. Mbeki's health minister, Manto Tshabalala-Msimang, was notorious for questioning the benefits of antiretrovirals and recommending garlic, beetroot and lemon as therapies for HIV. Her successor, Barbara Hogan, struck a different note, thanking "all the healthcare and community workers, activists, scientists ... and clinicians for spending enormous amounts of energy responding to AIDS in the last decade."

South Africa's Deputy President (before the recent election) Baleka Mbete told the conference that although South Africa has the world's largest free HIV treatment programme with 700,000 people on HIV drugs, 500,000 more were becoming infected every year. She said the South African health system needed a programme to address pandemic levels of rape in the society and specifically mentioned 'corrective rape' of lesbians as a reason to support marginalised people. She praised the opening of South Africa's first HIV clinic for gay men, in Cape Town.

South Africa faces huge challenges in continuing its HIV drug programme. However, the general atmosphere of the conference was one of pride that state and society are now at last working together to tackle the world's biggest HIV problem. Conference Chair Linda-Gail Bekker said: "It is high time to start pushing back the 'red zone' on maps covering southern Africa that indicate the high prevalence of AIDS and TB."

● For more on the Conference see coverage on aidsmap.com and visit www.saaids.com.

HIV testing

Increasing testing is theme at BHIVA Conference

A prominent theme of the British HIV Association (BHIVA) Conference in Liverpool in April was how to increase rates of testing and diagnosis. Palwasha Khan from east London's Homerton Hospital[1] reported that a project offering while-you-wait testing at their GUM clinic reduced the proportion of patients who refused an HIV test from one third to under one fifth. The rapid testing seemed to encourage high-risk people who had previously been scared to test: out of three positive diagnoses already made in the pilot programme, two were in people who had refused conventional testing.

While 96% of pregnant women get an HIV test, less than two-thirds of women attending the GUM clinic do. One way to reach out to women who might not consider themselves to have been at risk is also to offer HIV testing at pregnancy-termination clinics: the HIV rate in women requesting abortions is higher than in antenatal clinics. When an offer of an HIV test was included in Homerton's termination service, half the women attending took it up.[2]

One under-diagnosed group is the children of HIV-positive parents who come to the UK and were not HIV tested as babies. An audit at a clinic in Leeds[3]

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found that nearly 60% of the children of HIV clinic patients had not been tested for HIV. A similar audit in Glasgow[4] found that 42% of children who had emigrated from Africa and 12% of children born in the UK had not been tested. The Leeds researchers noted that parents may believe that if their child does not become sick they must be HIV-negative. Last December a one-day conference called *Don't Forget the Children*[5] was convened by the Children's HIV Association after a case in which a child diagnosed too late died at London's North Middlesex Hospital.

Several surveys looked at how quickly newly diagnosed people saw an HIV specialist and whether people dropped out of care post-diagnosis. BHIVA's *Standards for Clinical Care* recommend that patients should be seen by an HIV consultant within two weeks of diagnosis. An audit at Homerton Hospital[6] found that 93% of newly diagnosed patients were seen within a fortnight but that 35% of patients disappeared from care after attending this initial appointment, including a quarter of those with CD4 counts under 200 cells/mm^3. But a few miles away at Newham General Hospital,[7] only a third of patients were seen within the two-week target period and one in six had still not seen a specialist within six weeks.

Contraception

HIV-positive women need more contraception advice

Several surveys presented at the BHIVA Conference focused on the conception and contraception needs of women with HIV and found high levels of need for education around conception and pregnancy and low levels of use of contraceptive methods other than condoms.

A study from Leicester[1] found that a third of HIV-positive women had taken the decision that safer sex for them meant no sex. Of the remaining two-thirds, 65% used condoms as their only contraceptive method. Only 3% used the daily contraceptive pill (compared with 24% of HIV-negative women in the UK[2]) and 8% used long-lasting implant contraceptives. Use of these hormonal methods was low because of concerns about interactions with HIV drugs. The researchers recommend more use of long-lasting reversible methods such as the intrauterine device (IUD).

A study from a Birmingham clinic[3] found low levels of knowledge about HIV, conception and pregnancy amongst women with HIV. Eight per cent thought all babies born to HIV-positive women would be positive themselves. Only 42% knew that a caesarean section is not mandatory and only half knew that breastfeeding is not recommended.

A number of researchers[4] commented on the need for specific antenatal classes for women with HIV as so many of their medical needs are different from other women (for instance, most antenatal classes strongly promote breastfeeding) and discussing them would be difficult in a class for all women. The first antenatal class programme specifically for women with HIV has been introduced at North Middlesex Hospital and plans to help 30 to 45 women a year.

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Has HIV got nastier?

HIV may have evolved into a more agressive strain in the early years of the epidemic. Is it still happening? Asks *Gus Cairns*

A study published in this month's *Communicable Infectious Diseases* journal looks, on the face of it, worrying. "Has HIV become more virulent?" it asks, and decides that it has.[1] What this means is that researchers found that, in people recently infected with HIV, the first CD4 count measured after diagnosis has over time declined by over 100 cells/mm^3, from an average of 632 cells/mm^3 in the late 1980s to 514 cells/mm^3 today.

They also found that the proportion of people with a first CD4 count of below 350 cells/mm^3 (and therefore recommended to start HIV treatment straight away) had gone up, from one in eight patients then, to one in four now. And the proportion with CD4 counts below 200 cells/mm^3, – so immediately in danger of AIDS-related illness – had gone up from one in 50 patients to one in 20.

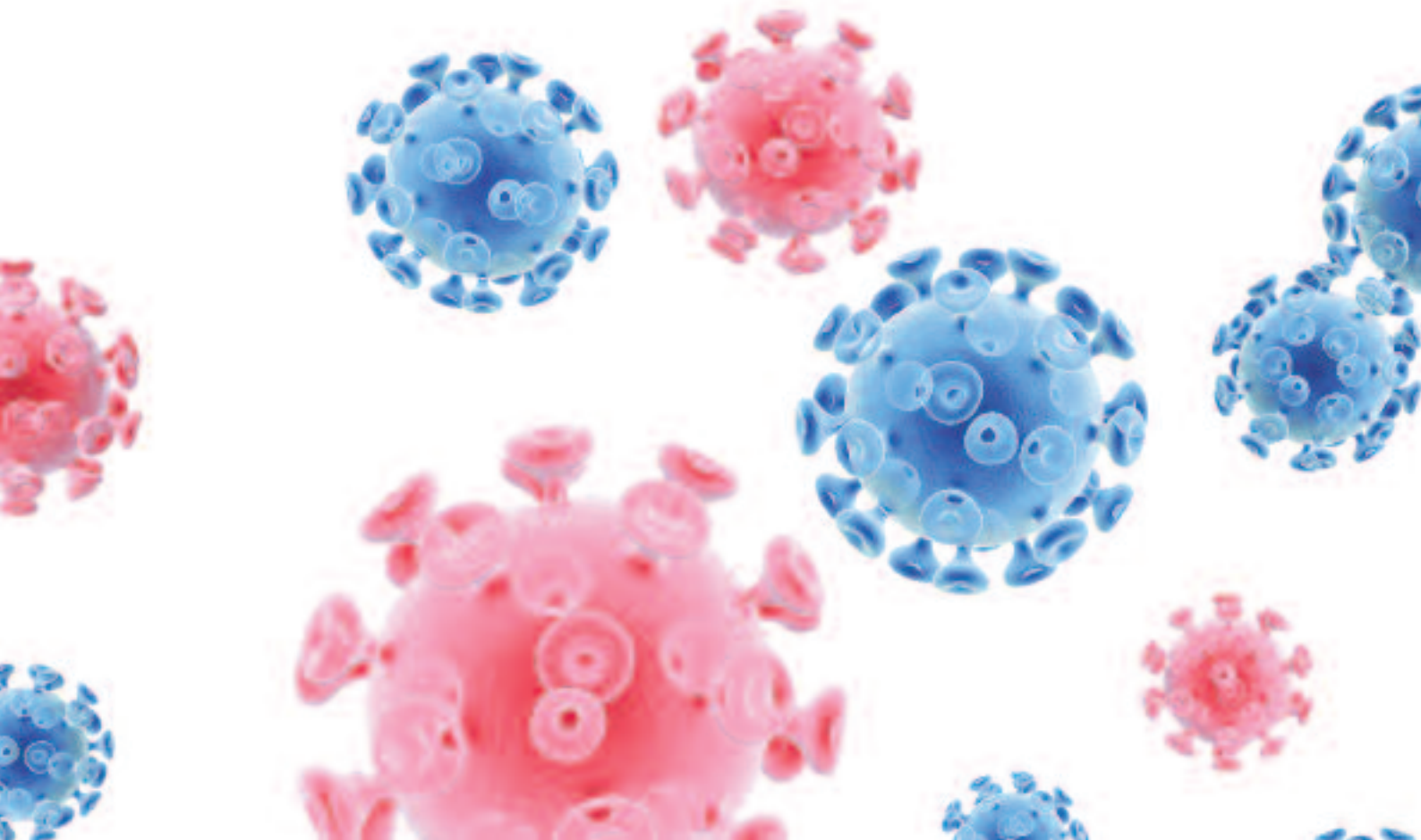
The implication, the authors said, was that HIV was learning to adapt to human immune defences. Might it get even better at doing so in the future? What does this imply for the figure of ten or so years often quoted as the time between HIV infection and developing AIDS – might it be getting shorter? And what would this imply for the number of people in the world who need to be on HIV therapy?

The problem with establishing if there has been a change in HIV's effect on CD4 counts is that many other factors might influence it. One obvious factor is whether the interval between infection and diagnosis has changed. Another might be if the race, age or gender profiles of the patients studied have changed over time. Black people tend to have slightly lower CD4 counts for their stage of infection than white people; older people have lower CD4 counts than younger people; and women have lower viral loads than men. If the patient group had changed, so might the initial CD4 count. Different patient groups also tend to have different types of HIV: some, like subtype D, common in east Africa, seem to be more aggressive.

The study solved this problem by looking at a group of people who all had an HIV test when they became members of the patient group studied, and then had regular HIV tests at least every four years thereafter – namely US army recruits. A test is mandatory if you apply to join the US Army (and you won't be accepted if you test positive). Serving soldiers are now re-tested every two years.

The researchers estimated the time of infection as the time midway between the last negative test and the positive test. They then took the first CD4 count measured after the positive test. The average time between HIV infection and testing positive was estimated as 17.5 months and this actually declined to 16 months by the end of the study. So the lower CD4 counts observed were not due to later testing.

Relative to the years 1985 to 1990, the average CD4 count post-diagnosis was 65 cells/mm^3 lower in the early 1990s and about 104 lower post-1996. Other



immune indicators declined too. The CD4 percentage (the proportion of lymphocytes, a type of white blood cell, that are CD4 cells, often seen as a longer-term and less variable measure of immune fitness) also declined from 30% in the late 1980s to 27% post-1996. So did the other kind of T-cells, the CD8 cells.

The other factors associated with a lower initial CD4 count were a longer time between infection and diagnosis, a higher viral load, being non-white and being older. But even though, for instance, the proportion of black recruits increased over the time of the study, this could not explain the decline in CD4 cells seen.

So should we all worry that HIV has for some reason started producing faster declines in T-cells? Probably not. There was no significant difference in CD4 counts between soldiers diagnosed between 1997 and 2001 and those diagnosed since 2002. Whatever caused HIV to apparently get nastier in pre-ART days, the start of HIV therapy seems to have halted that.

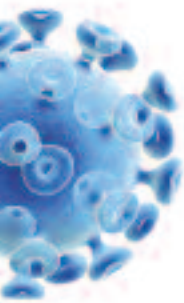
What might be going on? The researchers hypothesise that, in pre-treatment days, the ongoing battle between HIV and the body's immune system caused the virus to evolve into a more virulent strain. More often the opposite happens: diseases become less virulent as they go along – one example is syphilis – because the mutations (changes) they have to make to escape the body's vigilance make them less efficient at reproducing, just as some kinds of drug-resistance mutations do.

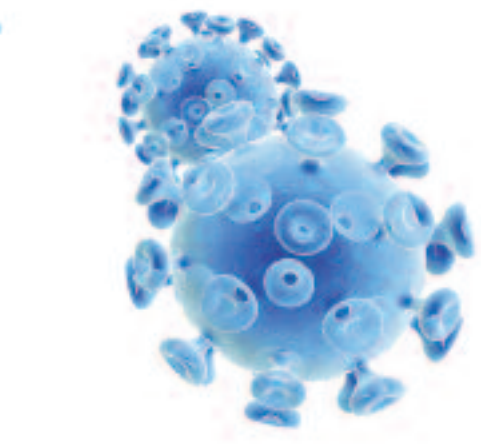
In the case of HIV, however, the opposite may have happened: only the fittest viruses produce high enough viral loads to make transmission frequent; it's a kind of 'bottleneck' that only the most forceful squeeze through. However by bringing viral replication down to near-zero in more patients, HIV therapy has made it less likely that fitter strains of HIV will keep arising.

Although a number of studies have found similar results, not all have. One from Belgium[2] measured HIV virulence in a very different way by taking varied samples of HIV from the early days of the epidemic and comparing their viral fitness with more recent samples by seeing how much virus was produced by test-tube cell cultures. It found that HIV had become *less* virulent over time. Other studies have found no change.

The recent study also, obviously, only looked at HIV in US patients. In another article,[3] the authors of the Belgian study note that, globally, HIV may be becoming a weaker virus because the strain that infects more than half the people in the world, subtype C, is in fact a more sluggish and less virulent type. This might partly explain some of the unexpected declines in HIV prevalence seen in some African countries. Another theory is that HIV has done a culling job on human beings, weeding out the weakest first: declines seen in prevalence and apparent infectivity in Africa and elsewhere may be due to HIV picking off the most vulnerable members of the population first.[4] The more robust specimens left may be better able to weather low CD4 counts.

What should we conclude from all this? HIV never ceases in its capacity to throw surprises at us, and because it reproduces a million times faster than human beings, it can change its nature very fast, as we have seen in drug resistance. So we can't afford to be complacent. At present, however, there is no sign that a strain of 'super' HIV is waiting for us round the corner. ■





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where to find out more about hiv

- **Find out more about HIV treatment:**
  NAM's factsheets, booklets, directories and website keep you up to date about key topics, and are designed to help you make your healthcare and HIV treatment decisions. Contact NAM to find out more and order your copies.
- **www.aidsmap.com**
  Visit our website for the latest news about HIV & AIDS, a fully searchable treatments database and a complete list of sexual health clinics in the UK.
- **THT Direct**
  Offers information and advice to anyone infected, affected or concerned about issues relating to HIV and sexual health.
  0845 1221 200
  Mon-Fri, 10am-10pm Sat-Sun, 12pm-6pm
- **i-Base Treatment Phoneline**
  An HIV treatment phoneline, where you can discuss your issues with a treatment expert.
  0808 8006 013
  Mon-Wed, 12pm-4pm