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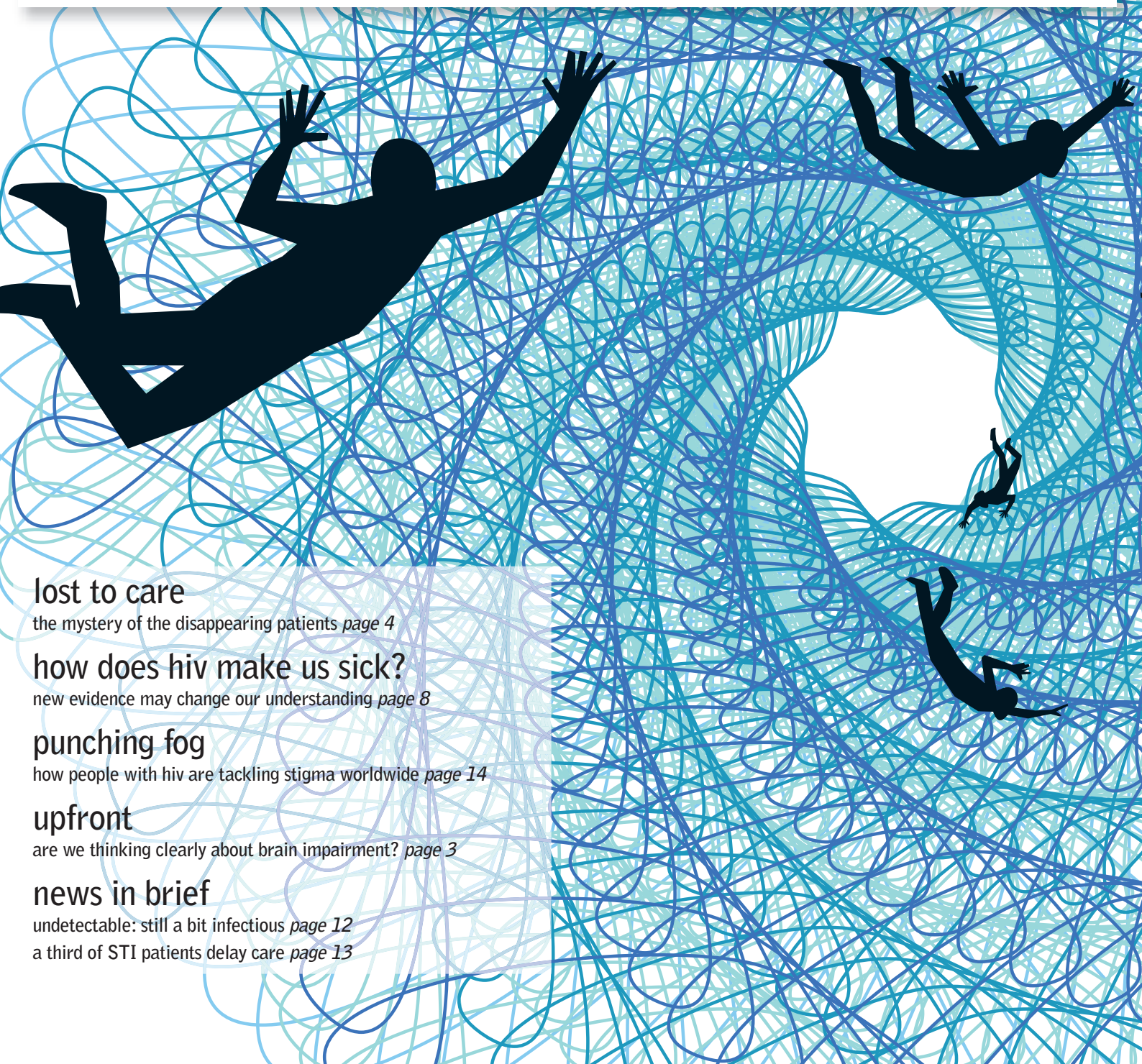
www.aidsmap.com
issue 191 november 2009

hiv treatment update



Gus Cairns

in this issue

At first sight this year's World AIDS Day theme might seem vague - 'Reality'. Well, yes, I suppose it's better to live in the real world, but what has it to do with HIV?

The answer is that the whole subject of HIV is surrounded by myths, outdated information, presumptions about the kind of people who get the virus and magic-bullet solutions to the epidemic, none of which have any basis in reality.

Every time a judge jails someone for passing on HIV because "HIV infection is a death sentence", they're living in a reality that's 15 years old rather than one of today. Equally, underestimating the difficulty of preventing HIV is also not facing reality. One example is to expect that testing everyone for HIV will provide a solution to the epidemic in itself.

Last month we looked at expanding HIV testing, but this month we find that receiving a positive test result is not the end of the story. As Chris Morley and I discover on page 4 (*Lost to Care*) a significant minority of people then disappear from HIV care, perhaps preferring to live in an unreality in which AIDS will never happen, just as they thought HIV never would.

While people's right to not seek medical support must be respected, it's possible that some patients may be scared off by myths and outdated information around treatment, such as the idea that all HIV drugs inevitably have awful side-effects. Others, having gathered the courage to test, suddenly find themselves defeated by the stigma and isolation they face and feel.

Many people vulnerable to HIV will never be completely happy to test, and many people infected will never be at peace about having the virus, until we see the end of HIV stigma. But, as we find out on page 14 (*Punching Fog*), stigma is a slippery concept. It's very difficult to fight something that saps the self-esteem of the fighter.

The solution the Stigma Index people came up with was radical: the problem is the solution. Get people with HIV to help other HIV-positive people to talk about their experiences. The victim of stigma becomes its chronicler. Do it in as many countries as you can. Then repeat the exercise every few years so you have a story of the way HIV stigma develops and changes over time. We hope funders will enable the Index to keep telling it.

If HIV was curable rather than just treatable, it might neutralise some of the stigma. As Derek Thaczuk discovers on page 8 (*How does HIV make us sick?*) scientists continue to probe the mystery of how a weak little virus gets its teeth into our immune defences and just won't let go. If we know, we might be able to prevent or eliminate HIV altogether, as we will explain in the next issue.

Till next time, our World AIDS Day wish for 2010 is more progress towards both a cure and a world without stigma. (See the back cover for details of how to support NAM this World AIDS Day.)

nam

hiv treatment update
editor Gus Cairns
sub-editing & proofreading Greta Hughson
design Rowena Weedon
printing Cambrian Printers
ISSN 17567890

charity number 1011220

hiv treatment update was founded by Peter Scott

contact details
Lincoln House, 1 Brixton Road, London, SW9 6DE, UK
tel: 020 7840 0050
fax: 020 7735 5351
email: info@nam.org.uk
web: www.aidsmap.com

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upfront

Are we thinking clearly about brain impairment?

For the last three years the UK's HIV doctors' and patients' organisations – the British HIV Association (BHIVA) and the UK Community Advisory Board (UKCAB) – have collaborated on bringing an issue of particular interest to patients to the autumn BHIVA Conference. This year, prompted by studies presented earlier in the year (see *HTU* 186), the subject was HIV-associated brain impairment and dementia.

Dr Simon Rackstraw, Medical Director of the Mildmay Hospital, spoke about the basic features of a condition which is often called 'HAND', for HIV-associated neurological disorder.

The incidence of severe AIDS dementia, a feature of very late-stage AIDS, fell from 3% a year in 1992 to 0.1% in 1998, and it was hoped would become virtually a thing of the past. So it was a shock to many when in 2009 the large US CHARTER study found that a *majority* – 53% – of patients had some evidence of neurological impairment.[1]

If HAND is so common, why haven't more of us noticed it? Possibly because the symptoms are so easy to blame on stress, lack of sleep or a hangover. They include:

- Difficulty concentrating and slowed thinking
- Difficulty remembering phone numbers/appointments, with reliance on reminders
- Irritability and depression
- Unsteady gait and poor co-ordination.

Rackstraw asked audience members if any of them had *not* experienced these symptoms at some point.

HAND and HIV dementia often improved with appropriate treatment, he said. Just putting untreated patients on antiretrovirals (ARVs) substantially reduces HAND. Antidepressants have also produced considerable improvements in patients with more severe neurological symptoms.

Mike Kopelman, Professor of Neuropsychiatry at King's College London, Institute of Psychiatry, added more details.

The exact definition of HAND is that patients are in the lowest 15.8% of the population, and of dementia in the lowest 2.2% of the population, when it comes to performance in at least two neuropsychological 'domains'.

Domains are areas of ability such as intelligence, memory, speed, focus, emotional stability and motor co-ordination.

Studies in both the pre- and post-ARV era, from 1992 and 2004, found that patients with HIV tended to have defects in recalling information, in fine muscle movements and co-ordination and in focusing and concentration. Other abilities such as abstract thought and memory of recent events tend to be less affected.

One interesting finding from a number of studies is that, in the short-term at least, HAND does not appear to progress. In one set of 32 patients observed for 27 months, mental performance got no worse during that time.[2]

It is not known, however, whether dementia awaits people further down the line. This concern was the motif of the third talk by Robert James of UKCAB.

Will we ever get to be old and wise? he asked. To find out, he canvassed people with HIV (some with diagnosed cognitive impairment and some without), support group leaders and professionals in the HIV and dementia fields.

Diagnosis was a common theme, with several people with impairment giving accounts of misdiagnosis. Simon Rackstraw commented that patients can be regarded by healthcare workers as 'difficult' or 'unco-operative' for years before it is finally found they have brain impairment. Problems with adherence may be a telltale sign.

If people with HIV were found to be more likely than the general public to develop dementia as they age, and earlier too, then social and healthcare provision for people with classic age-related dementias might not suit people with HIV, who will often be younger and more physically active.

Many patients and organisations were unaware of the issue of brain impairment, with patient groups saying that they had not seen it and that, unlike other mental health problems, it was not an issue. There was suspicion of assuming problems were neurological rather than psychological.

A post-seminar discussion produced a couple of specific recommendations.

In order to develop any sense of the frequency and course of brain impairment, all patients should be given a simple screening test at diagnosis. At present, because we do not have baseline screening, it is difficult to establish whether age or length of time living with HIV is the more important causative factor.

It was also recommended that as soon as the number of older patients allows, a cohort of patients over 65 should be established. At present over 50 is generally 'old' in HIV care, but patients older than this may need to be studied before we find out if many of us are going to lose our faculties as we age.

For the presentations from the seminar, see www.bhiva.org/cms1224475.asp

lost to care: the mystery of the disappearing patients

Up to a third of patients who attend their first HIV clinic appointment don't then return. Why do they drop out of care, and are they putting themselves in danger? *Chris Morley*, co-ordinator of HIV policy, information and publications at George House Trust in Manchester, and HTU's editor *Gus Cairns* investigate.

In the last issue of *HIV Treatment Update* we looked at ways to increase HIV testing in the UK and minimise the number of people who don't know their HIV status. However, there is not a lot of point in people learning their positive status if they then simply disappear from care.

How much does this happen, and does it matter? We already know that patients who are diagnosed after their CD4 count has fallen below 200 cells/mm^3 are eleven times more likely to die in the immediate post-test period than patients diagnosed sooner. [1]

If figures from France are anything to go by, it matters a lot. A study at five HIV clinics near Calais [2] found that over one in eight patients (13%) dropped out of care for at least a year.

Over half of those subsequently returned, after an average gap of 19 months. Nearly half of them, by that time, had a CD4 count under 200 cells/mm^3, and a quarter reappeared with an AIDS-related illness. And after the researchers controlled for the influence of patients' CD4 counts at diagnosis, they found that dropping out of care was associated with a more-than-fivefold increase in the chances of dying in the year after return, compared with people who had stayed in care.

We already know, from figures from the US, that 30% of people who take a rapid HIV test and get a reactive (positive) result fail to return for the necessary confirmatory test.[3]

London drop-outs

At least as high a proportion of patients in the UK as in the US seem to be disappearing from care. Last year, a study from King's College Hospital in south London[4] found that no less than 40% of patients seen at least once between 1995 and 2005 were not seen at all during 2006. Checking with the Health Protection Agency (HPA) found that half of these were attending another clinic and a small number were known to have died, but it still meant that more than one in five of all patients had disappeared from care. (The HPA encodes patients' surnames with a method called Soundex which, when combined with date of birth, creates a distinctive, though not necessarily unique, identifier which can be followed from clinic to clinic. No other identifying detail is kept.)

This year, several surveys from clinics in London were presented at the BHIVA spring conference in Liverpool with similar findings. One was from Homerton Hospital in Hackney, east London. This found that it was not patients failing to turn up for confirmatory tests that was the problem; instead, they were dropping out *after* this, once they'd had their confirmatory test and their first serious chat with an HIV consultant.

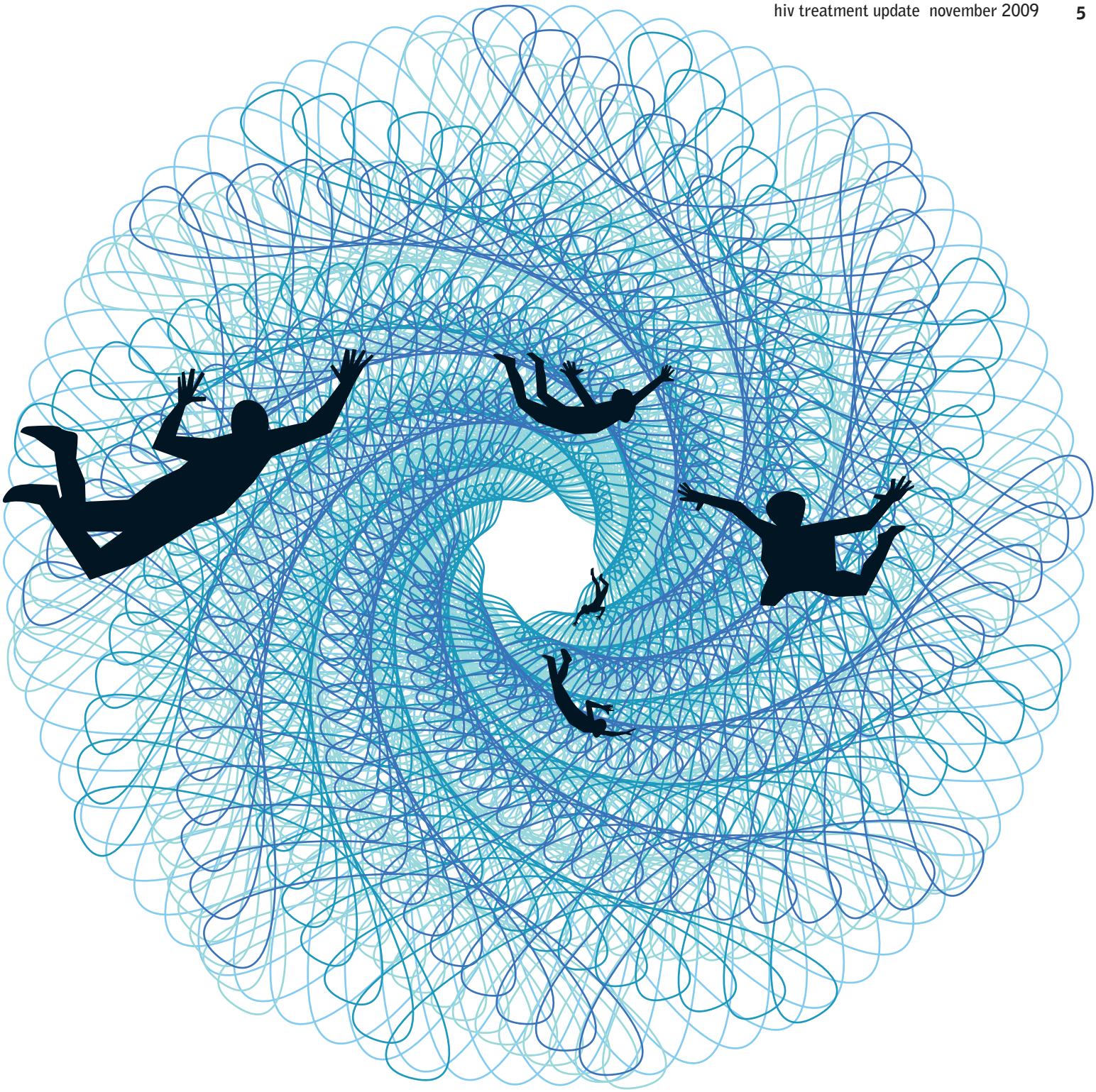
Only one out of 88 newly diagnosed patients failed to turn up for their initial HIV-clinic appointment after they had been diagnosed in other settings ranging from the GUM clinic to antenatal clinics, or by their GP. After that, however, over a third of the total failed to turn up for any subsequent appointment during 2007, including a quarter of the patients with CD4 counts under 200 cells/mm^3.

Dr Iain Reeves from Homerton comments: "We can't eliminate absolutely everyone who turned up at another clinic, as the Health Protection Agency data we use is very sensitive to misspelt names, wrong dates of birth, and so on."

Nonetheless, it's an ongoing problem, and has continued in 2009, he adds. If you take a shorter time-frame, you get better attendance, as cases are live and exclude people who have died or moved abroad.

"But," comments Reeves, "in our clinic population of about 700 we had 56 (8%) who we'd seen in the second half of 2008 who we didn't see in the first half of 2009. We found that ten of these had transferred to another clinic and five had died and we've managed to get about eight to come back by phoning them, but that leaves 33 patients who have completely vanished – nearly one in 20.

"If we've got a phone number or address, we'll try and contact them and if we've got permission to contact their GP, we will do that. In rare circumstances, if someone has been really seriously unwell, we may break confidentiality and contact their GP anyway, though I can only recall



a couple of cases. There is a dilemma between respecting patient autonomy and our duty to ensure the patient doesn't become seriously ill or die.

"People may have all sorts of reasons for not turning up. One of my patients was in prison and turned up again once he was out. But the two biggest reasons are depression and fear of stigma. There is a subset of patients who struggle with depression, have problems with adherence, and are very difficult to get into the clinic. With one recent patient of mine we counted it as a success that she'd phoned up to cancel her last appointment instead of just failing to show.

"Another lady was admitted here very ill and went straight to the Intensive Care Unit where she unfortunately died. Her partner tested positive here and then he disappeared too. When contacted, he said he had seen some people in the waiting room he thought might know him and he didn't want to be identified."

The North Middlesex Hospital, just a few miles away from Homerton, also did a survey, this time of long–term rather than new patients, and found that between 2005 and 2009, about 6% of the patient population disappeared every year. This figure excluded those known to have transferred, died, or moved out of the UK. It managed to trace 44% of those missing but could not establish where the remainder had gone.

Patients lost to care were on average somewhat younger, more recently diagnosed (two versus five years) and, worryingly, much more likely to have a detectable HIV viral load (60% versus 20%). Three times as many were on a failing drug regimen at the time they

disappeared from care, compared to patients who stayed in care.

The North Middlesex is now in the process of a systematic attempt to trace these patients. The hospital's Dr Chris Wood explains:

"We find the best results are to phone people's mobiles, as in our clinic population, many of whom are immigrants, their mobile numbers change less than their addresses. So far, we've managed to persuade everyone to re-attend that we've actually spoken to.

"Many are women diagnosed in the antenatal clinic. One recently phoned up and said she thought she had an appointment in November – after 2.5 years! I think she was embarrassed about not seeing us.

"Women sometimes prioritise their children's needs over their own, and may only show up again when they become pregnant once more: the way we imply that the purpose of testing is to avoid transmission to the baby may reinforce this.

"A lot test positive out of the blue, and feel perfectly well; in some ways they've never quite believed the test result. Some are in wilful denial, some genuinely don't know if they need to stay in touch, and some have very controlling spouses who don't want them to be in care.

"Another common reason is the dispersal of immigrants. Patients who don't make links with a clinic in their new area will drop out of care. It may have taken them a long time to trust a healthcare team and they don't want to go through it again.

"And yes, some believe they are cured. I had an east African chap who insisted he was. He said 'I know you won't agree with me, but I think I'm cured. I want a viral load test to prove it.' Well, we did the viral load test, which was high, and he still wasn't impressed by it!"

Missing in Manchester

This is not a problem restricted to London. The HPA has confirmed that over 300 people living with HIV in north-west England are missing from UK HIV clinics.

Around five or six years ago George House Trust in Manchester, the region's leading HIV community organisation, noticed that the number of new HIV cases was never matched by a similar rise in the total number of people documented as living with HIV: there was always an excess of new cases. Close study of the annual HIV reports[5] seemed to show NW England was steadily losing people with HIV, despite a rising population.

As long as only a few people went missing, this could be plausibly explained – for example, some people in Cumbria, in the north of the region, find it easier to go to Newcastle-upon-Tyne, and therefore out of area, for care.

But in 2007 the gap between new cases and the rise in the region's HIV total widened to more than twice the size it was before. George House Trust was concerned and wanted some answers. The staff there did a detailed analysis tracking the loss for each year since 1996 and then discussed their results[6] with the Centre for Public Health at Liverpool John Moores University, which produces the region's HIV statistics. John Moores confirmed that, while slightly over 100 were now attending clinics outside north-west England, there were more than 300 NW residents entirely missing from UK HIV clinics – that's 5% of the total diagnosed, as in London.

But patients lost by hospitals may not have disappeared from the community. Near the back of the annual HIV report is an interesting table that reveals that a third of the 2834 people living with HIV who used a community sector service in 2008 – a facility like George House Trust – were not in contact with any of the region's HIV clinics that year, and that fully one-quarter of people using community services have not been seen since diagnosis by a clinic in the region.

That represents an opportunity for community services to talk to their service users and find out if they are among the missing patients, and if so why – and what they feel their needs are.

For instance, we can see that among the nearly 300 asylum seekers using community services in 2008, a third had never been seen by a clinic since diagnosis and 40% made no contact during 2008. UK nationals do somewhat better, but just under 30% made no contact. People from any minority ethnic group are more likely to be missing from clinics than white people, but 29% of white people had no clinic contact either.

Over a quarter – 27% – of gay men who used community sector services were unseen by clinics in 2008 and more than half of these men have never been to a NW-region HIV clinic since diagnosis.

Finally, a startling 60% of children and young people with HIV who are in touch with community services – that's 40 out of 67 young people – have never been seen since diagnosis by a clinic in the region. Yet both Manchester and Liverpool have specialist regional paediatric hospitals.

People who've never used a NW England HIV clinic since diagnosis are more likely to be male than female, and heterosexually infected rather than gay men (53% compared with 39%). Conversely, however, people who had not turned up in 2008, having been seen in the previous year, were more likely to be gay white UK nationals.

This apparent contradiction can be explained if vulnerable and marginalised people (especially women diagnosed in pregnancy and young people) are more likely to drop out of care altogether after diagnosis, and are only forced back by sickness, yet good CD4 counts result in people deciding to take a break from care – hence the shorter-term absence of gay men.

We are doing better than we were. HPA research suggests being lost to follow-up is a stage many people go through and that the proportion of clinic drop-outs was once much higher, especially before effective HIV therapy became available. The estimated drop-out rate plunged from 14% before combination therapy, to 6.3% in 1998, and then gradually fell to 3.8% in 2005.[7] Almost everyone appears (or reappears) for HIV clinical

care at some stage. In London, Chris Wood comments that "people often show up after a gap of three to four years."

Why do people drop out?

Tables and studies can't tell us anything about the reasons people don't use clinics. One of us (Chris) talked to several people at George House Trust who identified themselves as former or current drop-outs.

Here's an example:

"*When I was diagnosed back in '93 there was still a 'death sentence' attitude both from clinical staff and other positive people I knew. I remember being told by the nurse to make the most of the time I had left, and the doctor wrote me a DS1500 [people expected to die within about six months can use this to claim Disability Living Allowance immediately]. It was another six years before I went back to clinic, after having somewhat of a wild time in between, I realised I hadn't kicked the proverbial [bucket = died], but was starting to notice higher levels of fatigue, which prompted me to go back.*" (White gay man, mid 40s)

Talking with people living with HIV reveals a wide range of reasons why people become lost to follow-up. People often have several reasons and these may shift over time. One man, who was diagnosed this May, has an aversion to needles and lacks suitable veins for drawing blood, and has now given up on the clinic because he feels he's "*been roughly handled and not given respect and privacy*". He's also "*depressed and anxious and [doesn't] want to stress about my CD4*".

Few people see HIV as a purely clinical issue in their lives. For some people no amount of clinical good advice and reasoning will work because this simply doesn't fit their frame of reference for understanding and living life. For some people, for example, unless drugs and their taking are explained and legitimised in biblical terms or other references that fit with their beliefs, they may not take treatment. Unless we understand and engage with people's individual socio-cultural beliefs, the chances of engaging and retaining the person in clinical care are diminished.

Chris Morley makes six recommendations to reduce the number of patients lost to care.

1. We need to better understand the reasons people drop out of care. These could include stigma, shame, fear, disbelief, misunderstandings about HIV and treatment, mental ill-health, adverse life circumstances, conflicts with the individual's socio-cultural beliefs and not prioritising HIV in a busy life.
2. The HPA needs to improve its analysis of people who drop out and should feed back anonymised details to HIV clinics and community organisations.
3. Community research among people living with HIV is needed, to find out exactly why and for how long people drop out of care after diagnosis.
4. Organisations like the British HIV Association and the London HIV Consortium could audit HIV clinics for patient retention.
5. Good practice guides developed by organisations like BHIVA and further training can help clinics to predict likely drop-outs and meet their needs better.
6. Community organisations need to be aware that many of their service users may not be attending clinics and take steps to identify and better support them.

There are other reasons for drop-out, such as impractical clinic hours not geared to those with jobs:

"*I book an early appointment to minimise time off from work but am always made to wait at least an hour; pharmacy home deliveries don't arrive as booked although I have taken time off for these; and I can't give bloods for convenience at my GP. The service has a 'take it or leave it' attitude, one size fits all.*"

People clutch at bits of HIV good news and are ignorant about or disregard much else they may hear. In the midst of the shock of diagnosis, there is evidence of selective listening and over-simplistic reassurance, and both contribute to drop-outs.

People gave us lots of examples of what might be called over-enthusiastic reassurance. We've heard: "You are more likely to be knocked down by a bus than die of HIV", "You'll probably live to 95", "Your CD4 is 650 and you won't need to start treatment for years", and the classic "With modern treatments it's just a long-term condition like diabetes".

The problem with giving such reassurance is that in people who are already highly anxious about HIV it can become fuel for denial. Reassurance needs to be tailored to the individual. It's often misplaced and misread, and taken as permission to put HIV aside and drop out of care.

Community organisations often spend time unpicking and correcting inaccurate or incomplete messages seared into people's brains in the trauma of diagnosis. What people actually hear when HIV is compared with diabetes is: "You'll live a more-or-less normal life".

Ordinary people are unlikely to know that successful long-term diabetes care requires significant lifestyle changes in diet, weight control, alcohol use, self-testing of blood-sugar levels and medication management, and that if you don't adhere to these you can lose your sight, have serious kidney problems, develop gangrene and need amputations. People aren't told or don't hear the full diabetes comparison story – that many people fail to achieve proper diabetes self-care and pay the health consequences.

When people are lost to follow-up with HIV, we need to make it plain there will probably be a price to be paid in worsened health. Clinics need to be scrupulously accurate and fully explain what they are saying because people traumatised by bad news won't always absorb information reliably. ■

How does HIV make us sick?

Nearly 30 years after the first documented cases of AIDS, we still don't know exactly how HIV destroys the immune system. But inflammation – sustained immune activation – is now seen as a key factor in how it wreaks its damage. Investigation into this is revising the way the virus is understood – and how it might be treated. *Derek Thaczuk* reports.

The end results of HIV infection have been clear since the epidemic began: left untreated, the virus eventually causes a massive loss of CD4 cells, pivotal players in the body's immune defences. If CD4 cell counts fall low enough, the body becomes prey to opportunistic infections and cancers which the previously healthy immune system could defeat.

Perhaps surprisingly, though, we still don't completely understand *how* HIV depletes CD4 cells. Also, while antiretroviral treatment has allowed HIV-positive people to maintain healthy CD4 counts, all but vanquishing life-threatening opportunistic infections like cytomegalovirus (CMV) and *pneumocystis* pneumonia (PCP), metabolic problems such as cardiovascular and kidney disease remain widespread. The toxicities of antiretroviral treatment – such as increased cholesterol levels – do not fully explain such complications: HIV infection itself is now understood to significantly raise metabolic risks.

Several emerging concepts may shed light on these questions. Inflammation – the prolonged state of immune activation resulting from the immune system's ongoing battle with the virus – appears to be a key factor in metabolic disorders and cardiovascular disease. Research is also finding that the digestive tract may play a much larger role in HIV disease progression than previously realised, and in fact may be one of the sources of immune activation.

Early infection and the gut

The course of HIV infection follows a largely characteristic pattern in most people. During the first few weeks – acute infection – the immune system has not yet learned to respond to the new intruder. HIV levels are high throughout the body, and the number of CD4 cells in the blood plasma sharply drops.

Evidence now suggests that, by only looking at CD4 cells in the blood, we may have underestimated the overall extent of this early drop. Only a small fraction (2%) of the body's CD4 cells are actually found in circulating blood. Most live in lymph nodes (these include the 'glands' you can sometimes feel in the neck and groin when you have an infection), in the gut-associated lymphoid tissue (GALT), where they are present as patches of immune cells lining the length of the gut, and in the mucous membranes lining other organs exposed to foreign substances, such as the lungs and the genitals. Researchers have observed a massive loss of CD4 memory cells (see over for this and other terms) in this gut tissue very early after infection.[1]

Danny Douek, a researcher at the US National Institute of Allergy and Infectious Diseases (NIAID), has studied the process closely: "Once we thought that CD4 cells were lost slowly but surely over the course of the disease. But we are now seeing that most of the memory T-cell pool – which is most of the CD4 cell pool in an adult person – is lost extremely rapidly." Roughly 60% of memory cells may become infected, and the majority of those may disappear within the first two weeks of infection.

Besides stripping the tissue of so many CD4 cells, HIV also causes structural damage to the gut immune tissue and to the lymph nodes where many immune cells normally reside. Recent studies have found that these tissues become scarred with collagen tissue during acute infection.[2] Researchers speculate that this damage interferes with normal cell growth and interaction, limiting the immune system's ability to fully regenerate the CD4 cells lost in early infection. Gut tissue damage may also contribute to the inflammation that helps drive the later stages of HIV disease – a point we'll return to.[3]

Chronic infection: why do CD4 cells die?

After the intense few weeks of acute infection, the body begins to produce antibodies and immune cells that specifically target HIV. During this period (known as seroconversion), viral load levels drop and the CD4 cell count returns to near-normal levels. At this point, the disease enters a prolonged phase known as chronic infection.

In the early years of the epidemic, the virus was even thought to lie dormant during the lengthy period of chronic infection. This proved completely wrong: the advent of viral load testing in the mid-1990s proved that the virus continues to actively infect CD4 and other cells from the moment of infection onward, producing millions of new copies every day.

Is the virus directly killing off CD4 cells? It's easy to assume that must be the main reason for the eventual drop in CD4 counts. The truth, however, is more complex. Considerably less than 1% of circulating CD4 cells are actually HIV-infected during chronic infection – far

effects brush: www.obsidiandawn.com

too few to explain the overall loss – and millions of new CD4 cells are created every day. In recent years, researchers have uncovered other possible means by which HIV leads to loss of CD4 cells. These include toxic viral proteins, spewed out by infected cells, which can kill off uninfected cells in a so-called 'bystander effect'. HIV can also trigger cells into 'committing suicide' in a process called apoptosis, or programmed cell death.[4]

Other mechanisms are likely to be at work as well, including – ironically – the immune system's own response to HIV. The virus can only infect *activated* CD4 cells – those that have been 'switched on' to fight against infection. In other words, by the very act of going into action against the virus, CD4 cells make themselves targets for it. This paradox is unavoidable to a certain degree, since immune cell activation is an essential part of immune function. However, there is growing evidence that prolonged and excessive immune activation – inflammation – underlies much of the ongoing damage of HIV disease.[5]

Immune overdrive

The idea that inflammation plays a major role in HIV disease was first proposed in the late 1980s,[6] but has taken centre stage only recently. One of the first major clues came from the SMART study. This large-scale trial investigated whether people who remained on continuous antiretroviral therapy fared better or worse than those who took structured treatment interruptions – stopping treatment when their CD4 counts climbed above 350 cells/mm^3 and resuming it when their counts fell below 250 cells/mm^3.

The SMART study was halted early after interim results clearly showed that people interrupting their treatment were over twice as likely to become seriously ill or die. Tellingly, treatment interrupters were not just at risk of 'traditional' opportunistic infections. They also had higher rates of heart, liver, and kidney diseases – metabolic problems that are often associated with inflammation. If HIV was driving up levels of immune activation, we would expect to see more inflammation-related diseases in people whose HIV was allowed to replicate – just as was seen in SMART.

Further studies have confirmed that immune activation is actually a very good way to predict how fast HIV disease is progressing. People with higher blood levels of a substance called C-reactive protein (CRP) – known to be a sign of immune activation – progress to worse stages of AIDS more quickly than those with low levels. (CRP is, in

fact, a much better predictor of progression than HIV viral load.)[7]

Why, then, does immune activation persist after treatment, instead of falling to near-normal levels when HIV replication has been controlled by antiretroviral treatment? Thus far, this is one of the most speculative areas of the hypothesis. Yet many researchers are convinced that the answer lies back where we began – in the infected tissues of the digestive tract.

Back to the gut

The lymphoid tissue in the gut keeps watch on microbes in the digestive tract – whether disease-causing organisms from contaminated food or water, or the 'friendly' bacteria that colonise the gut and aid digestion, mounting responses that keep the microbes out of the bloodstream. As discussed earlier, the lining of the gut can sustain lasting damage early on during HIV infection, becoming permeable or 'leaky'.[8]

Danny Douek explains: "The outer wall of most bacteria in the gut contains what's known as endotoxin, or lipopolysaccharide (LPS). LPS is extremely immunostimulatory. In people with sepsis or toxic shock, you see an overwhelming immune activation due to huge amounts of LPS in their systems. In people with HIV infection, we have found LPS in the bloodstream – not in the same amounts as in sepsis, but enough to activate immune cells. We have also measured elevated levels of other bacterial products, all of which are immune activators, in the bloodstreams of people with HIV infection."

This hypothesis, known as microbial translocation, is currently one of the leading explanations for the persistent immune activation seen in HIV infection.[9] However, many researchers suspect that immune activation has many causes. "I'm not convinced that microbial translocation from the gut is the sole answer to HIV-related inflammation," says Robin Weiss, professor of viral oncology at University College London. "We also see sustained immune activation in malaria, and nobody is proposing gut microbes as the source of that." Other candidates for drivers of HIV progression may include the immune stimulation caused by other infections, and the depletion or disabling of regulatory T-cells, which play a key role in cooling down immune activation. Immune cells also produce a variety of 'messenger chemicals' known as cytokines, which alert other cells to adjust their immune activity. HIV may confuse this immune communication network by disrupting cytokine production.[10]

As well as disentangling these complex processes, researchers must also investigate one of the biggest remaining questions: why HIV-positive humans are not able to correct excess immune activation, as they do with other chronic viral infections such as hepatitis C, or as simians (monkeys) are able to do with simian immunodeficiency virus (SIV).

LTNPs and elite controllers: why does HIV not progress in some people?

For reasons that are not well understood, a minority of HIV-positive individuals – 'long-term nonprogressors', or LTNPs – maintain high CD4 cell counts much longer than most. One particularly fortunate group, the so-called 'elite controllers', are able to keep HIV viral load at undetectable levels with no antiretroviral or other treatment.

One reason may lie in the immune system's CD8 cells, which control HIV by destroying infected cells. In most infected individuals, CD8 cells are present in high numbers yet seem unable to properly respond to HIV. LTNPs may be blessed with CD8s that remain able to strongly attack HIV-infected cells. The reasons for this are likely to be genetic.

In fact, many genetic differences between individuals can affect vulnerability to HIV infection and the speed of disease progression. For instance, to infect a CD4 cell, HIV needs to latch on to two specific pieces of the cell's surface – the CD4 molecule itself, plus one of two 'co-receptors' called either CCR5 or CXCR4 (the majority of virus uses CCR5). A small percentage of people lack one or more of the genes needed to make CCR5. In people with a single missing gene, HIV disease develops much more slowly: such people have fewer CCR5 molecules, giving HIV fewer targets. Those who entirely lack the CCR5 genes seem altogether immune to the vast majority of HIV strains and indeed we now have a drug, maraviroc *(Celsentri)*, that mimics

TYPES OF IMMUNE CELLS

The immune system is a complex array of different cells that do different jobs.

Some mount fast, non-specific reactions such as **allergies** to get rid of foreign substances.

Some, the **monocytes**, engulf and sometimes digest invaders.

B-cells secrete **antibodies**, proteins that surround specific invaders and either physically block them from infecting cells or flag them for destruction.

T-cells divide into **CD8** cells, which destroy already infected cells, or **CD4** cells, which regulate and amplify other parts of the immune response.

Both B- and T-cells can be **memory** cells, sensitised to specific invaders for a quick response to them in the future. Vaccines work by priming this memory.

B- and T-cells can also be resting or **activated**. Activated cells work at infection sites, and they are short-lived.

One theory of how HIV slowly destroys the immune system is that it causes too many T-cells to stay in a permanently activated state, and thus 'exhausts' this branch of the immune system.

this situation by blocking off people's CCR5 receptors.

Other genes called things like *TRIM* and *APOBEC* control other immune defence mechanisms that interfere with various aspects of the life-cycle of viruses (not just HIV). HIV has in turn developed counter-defence genes like *nef* and *vif* that neutralise these cellular defences – but we could develop drugs that in turn block these genes and allow the cell to control HIV. Natural variations in these genes may explain why some people control their infection more effectively, and may influence the sensitivity of different populations to infection – the mutation that deletes the CCR5 gene, for instance, occurs in about 1.5% of northern European Caucasians but virtually no black Africans.

What lies ahead?

Regardless of the immune stimulation that seems to help drive HIV disease, in the end we are trying to avoid the opposite – the immune *deficiency* that leaves people vulnerable to fatal opportunistic infections. Ideally, HIV treatment may need to guard against both immune deficiency and stimulation. This is likely to be a complex goal, and the consensus is that considerable research is still needed.

McGill University's Jean-Pierre Routy believes that, in order to reduce cardiovascular risk, comprehensive HIV treatment "will need to reduce inflammation, not just control viral replication". How we do that will almost certainly include a push toward starting treatment earlier, but "adding anti-inflammatory drugs to antiretroviral treatment may be the best way to prevent long-term immune hyperactivation". Clinical trials of anti-inflammatory agents such as chloroquine are set to begin, but such trials will need to be conducted cautiously so as not to induce the wrong kind of immunosuppression.[11]

What role, then, for 'immune-boosting' treatments such as interleukins? Large and very long-term trials of interleukin-2 (IL-2) recently concluded that, despite raising CD4 counts, IL-2 resulted in no net long-term improvement in the people who took it. Indeed, people who received IL-2 were more likely to develop serious illnesses, especially an array of blood vessel and cardiovascular problems that are probably due to inflammation. However, there are dozens of interleukins and other cytokines governing the immune system, and interacting with each other: 'immune-boosting' and 'immune-suppressing' are likely to be oversimplified ways of viewing such a complex network. Says Routy, "We didn't have this understanding of HIV and inflammation when the IL-2 trials were designed twelve years ago. There may be different benefits with IL-7 or other cytokines."

An earlier start to HIV treatment

While many details remain to be investigated, consensus is growing around one key point: the need for earlier antiretroviral treatment. If ongoing HIV infection poses greater future health risks than HIV treatment does – as SMART and other studies suggest – then earlier treatment would be warranted. Large comparisons of cohort studies are finding that, as treatment is started at higher CD4 counts, the risk of AIDS-defining illnesses or death steadily decreases. The trend holds true up to beginning treatment at CD4 counts of 350 cells/mm^3, although the benefits of starting treatment at even higher counts are less clear.

Is the case for earlier treatment persuasive enough to change treatment decisions for people with HIV? As an example, Richard Carson, diagnosed in 2005, is uncertain. By current treatment guidelines, Richard's robust CD4 counts (635 cells/mm^3 at last count) and low viral load (1550 copies/ml) have allowed him to look at antiretrovirals as a distant prospect. He has heard the earlier-is-better arguments, but is not quite prepared to jump into treatment as a result. "In the end, I'll do whatever is best for me," he says. "I've heard a lot of reasons why I should not start treatment yet – the side-effects, the risk of resistance. If there's more solid evidence that I shouldn't wait, then I may change my mind."

One final challenge may be simply trying to accommodate new evidence and new insights into a pre-existing model that no longer fits. CD4 cell depletion has often been understood by a simple 'tap and drain' analogy: picture the CD4 cell count as the level of water in a sink, with the drain open and the tap running. CD4 cells are destroyed as they are infected by HIV (the drain), but replenished as the body produces more (the tap). When the tap can no longer keep pace with the drain, CD4 counts fall.

As we realise the many factors that affect disease progression, will it be hard to abandon this simple picture for a more complex, if more accurate one? Danny Douek thinks not: "I don't necessarily think that more accurate means messier and more complicated. The original model of a tap and drain is actually a pretty good model. I think we've simply realised that there may be more taps and more drains. I think the model still stands pretty well, but it's becoming more complete and sophisticated. Ultimately it will be simpler because it will make more sense and leave less unanswered." ■

GLOSSARY

Cardiovascular disease: Disease of the heart or blood vessels, such as heart attack and stroke.

Cytokines: Chemical 'messengers' exchanged between immune cells that affect the function of the immune system. Interleukins such as IL-2 are a particular type of cytokine.

GALT: Gut-associated lymphoid tissue – an immune-cell-rich mass of tissue found throughout the mucous surfaces of the digestive tract.

Lymph nodes: Bean-sized structures throughout the body's lymphatic system, where immune cells congregate to fight infections.

Pathogenesis: The origin and step-by-step development of disease.

Receptor and co-receptor: HIV needs to physically attach to two proteins that sit on the surface of a cell in order to infect the cell. The first is the CD4 molecule: once HIV is tethered to this, it pulls itself in nearer to the cell by binding to one of two co-receptor proteins, CCR5 or CXCR4.

news in brief

Europe

STI screening lets UK down

A study of 29 European countries, assessing their HIV policies and services, has found that Luxembourg has the best response to HIV in Europe, while Romania has the worst.[1] The UK came in ninth, with excellent marks for medical care and good ones for prevention. But it was marked down because it does not have compulsory sex education, because of perceived discrimination, and because HIV patients said regular screening for STIs and hepatitis was not automatically performed.

The top five nations were Luxembourg, Malta, Switzerland, Finland and the Netherlands, while the bottom three were Italy, Greece and Romania.

The Brussels policy unit Health Consumer Powerhouse (HCP), assessed policy and outcomes in areas of HIV prevention (such as testing policy and rates, harm reduction for drug users, and sex education) and in areas of care such as access to drug-resistance testing and health care for migrants.

Poor collection of statistics prevented them reporting on indicators such as proportion of people diagnosed late and availability of antiretroviral drugs.

The survey also collected data on discrimination (perceived rather than actual), the criminalisation of transmission and other social policies.

The fact that the UK was marked down badly for access to STI and hepatitis screening for patients with HIV shows differing perceptions between healthcare workers and patients. BHIVA's sexual health guidelines recommend regular screening, but most patients and activists surveyed said that, in many clinics, patients had to ask to be screened.

Adherence

Full adherence less crucial over time

Patients who have had an undetectable viral load for over a year may be able to miss a quarter or even half their doses of therapy without it failing, a US study has found.[1] However, it found strict adherence was necessary during the first months.

The study looked at 221 patients between 1998 and 2007. Average adherence was good, at 92% – the equivalent of forgetting one dose about every twelve days on a once-daily regimen – and all patients initially achieved an undetectable viral load. However nearly half experienced a subsequent 'rebound' in their viral load.

These treatment failures were nearly all in patients who had poor adherence early on in their therapy. Half of all patients whose adherence fell to 50 to 75% in the first month after they initially became undetectable experienced subsequent drug failure. If, however, they had successfully suppressed HIV for a year, then having an adherence level of 50 to 75% at the end of that year was only associated with a 2% risk of failure.

Nevertheless, the researchers cautioned that the goal of near-perfect adherence should remain unchanged.

HIV and cancer

More cancers with CD4s below 500

The risk of six of the seven most common cancers seen in people with HIV is raised in patients with CD4 counts as high as 500 cells/mm^3, compared with patients with counts over this figure, a French study has found.[1]

The paper will strengthen the suggestion that antiretroviral therapy has significant health benefits in people with CD4 counts below 500 cells/mm^3 – the vast majority of diagnosed patients.

The seven cancers were Kaposi's sarcoma, non-Hodgkin's lymphoma, cervical cancer (all AIDS-defining in people with HIV), anal cancer, lung cancer, Hodgkin's lymphoma and liver cancer.

Researchers used records of over 52,000 patients to establish the risk of these cancers and relate them to CD4 count, viral load and antiretroviral treatment.

The first two cancers were the most common and associated strongly with a CD4 count below 200 cells/mm^3, not taking ARVs, or ARV failure. Cervical cancer was also associated with a CD4 count under 200 cells/mm^3 and not taking ARVs.

In contrast, most, of the patients with non-AIDS defining cancers were on effective ARV therapy. Past rather than present viral and immune status had the strongest influence on these.

The risk of all cancers (except anal cancer) was lower in patients with CD4 counts over 500 cells/mm^3 than in patients with CD4 counts between 350 and 500 cells/mm^3.

The investigators note that "immunodeficiency increased the risk of all cancers that we investigated," though in different ways. They emphasised that prompt diagnosis of HIV and starting ARV therapy would cut this risk.

Infectiousness

Undetectable: still a bit infectious

A large African trial involving partners of different HIV status has enabled US researchers to estimate the degree to which reducing a person's blood viral load reduces their infectiousness.[1]

Dr Jairam Lingappa and colleagues from the University of Washington in Seattle

found that a 5.5-fold (0.74 log) reduction in a person's viral load would halve the risk of their passing on HIV.

This implies, for instance, that if a person starts with a fairly average viral load of 46,000 copies/ml and we presume they pass on HIV once in 350 sexual contacts – typical of vaginal intercourse with a chronically infected partner – then reducing their viral load to undetectable (under 50 copies/ml) would reduce that chance to once per 5600 contacts.

These figures come from an analysis of the Partners in Prevention study, which looked at sero-different couples and gave the HIV-positive partner the anti-herpes drug aciclovir to see if it reduced HIV transmission. The study failed in this primary aim; but, because it was a study of couples, the researchers could know with reasonable accuracy who infected whom and when, and had measured viral loads quite close to the time of transmission. There were 108 HIV transmissions between 1704 couples during the study.

The chances of transmission were related to the HIV-positive partner's viral load. There was an approximately 5% chance of HIV transmission per year from partners with viral loads over 100,000 copies/ml; about a 3% chance with viral loads over 10,000 copies/ml; and a 0.3% chance with viral loads lower than 1000 copies/ml.

The transmission rate in the study was lower than average for an African population. Giving a more typical population ARVs to reduce their viral load might result in a greater reduction in transmissions.

Sexual health

A third of STI patients delay care

Over a third of patients who contact genitourinary medicine (GUM) clinics turn down appointments offered to them in the next 48 hours, a study has found. Nearly half of these patients have symptoms of a sexually transmitted infection (STI). The study revealed a widespread misapprehension that delaying treatment did not pose risks to health.

Researchers from the GUM clinic in Chester questioned 110 patients attending the clinic and 138 former patients on the phone. One in six patients attending the clinic and more than a third interviewed by phone recalled having turned down an immediate appointment. Work commitments were by far the most common reason given for delaying the appointment beyond 48 hours.

Despite the fact that untreated STIs can become more serious, 39 out of 80 clinic respondents and 51 out of 60 phone respondents felt that delaying appointments posed no health risks.

The researchers said they accepted patients wished to choose an appointment but commented that this choice should be an informed one.

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punching fog – how people with hiv are tackling stigma worldwide

The UK theme of this World AIDS Day is 'HIV: Reality', building on last year's theme of 'Respect and Protect'. The reality is that HIV status continues to mark people down as second-class citizens worldwide. *Gus Cairns* looks at a community-led initiative that documents HIV-positive people's experience of stigma and helps them combat it.

HIV is a stigmatised condition, it's agreed. To reveal one's HIV status risks disapproval, rejection or worse. People may also stigmatise themselves, blaming themselves for having the virus.

How to reduce stigma is less clear. While we can legislate against discrimination, tackling attitudes is much harder.

Anti-stigma initiatives may have all the effect of punching fog unless we understand exactly what we are trying to combat and how we can.

Stigma describes something we attach to people perceived as having offended against the way we think people *ought* to be.

The US sociologist Erving Goffman, in his seminal book,[1] described it as an intensification of the normal expectations we have of people.

"We lean on these anticipations we have," he said, "transforming them into [...] righteously presented demands."

Who's this 'we'? Well, it's unlikely anyone is free of stigmatising attitudes towards others. What do you think of bonus-grabbing bankers? Of AIDS denialists? Even members of a stigmatised group can stigmatise others, and quite often we do to those nearest us. In June, *HTU* looked at how having HIV is stigmatised by gay men (see *Stigma Begins at Home*, issue 187).

Yusef Azad is Director of Policy and Campaigns for the National AIDS Trust (NAT), which has campaigned against both stigma and discrimination in the past. Azad now makes a careful distinction between three concepts.

"**Discrimination** is the simplest of the three to tackle," he says. "It is a legal concept, a concrete and identifiable way of doing harm to someone by treating them differently. It may be the result of prejudice or stigma but you don't have to look at motivations or reasons to prove discrimination.

"**Prejudice** consists of unfair, stereotypical and usually negative assumptions about someone else based on the group they are seen to belong to."

Prejudices may still not be stigma. "Stigma is different because it has a concept of shame attached to it," says Azad.

"In **stigma**, a belief system is actually *shared* by the stigmatiser and the stigmatised. The stigmatiser fears becoming the type of person they hate, and the stigmatised person feels [that] shame... Stigma has a grip on people: that's what's so toxic and unfair about it.

"Stigma is absolutely dependent on the stigmatised person actually giving a damn, in terms of feeling ashamed," says Azad. "Organisations like NAT can combat discrimination, and we can even help to make public expression of stigma unacceptable. But the only thing that stops stigma is for people with HIV to refuse to feel the stigma. Why should they have to do this? Because only they can."

Conscious of this, a group of HIV–positive activists have developed an ambitious project to measure, describe, codify and combat stigma against people with HIV: The People Living with HIV Stigma Index, a joint project of the International Planned Parenthood Federation (IPPF), the Global Network of People Living with HIV and AIDS (GNP+), the International Community of Women Living with HIV (ICW), and UNAIDS.

The Stigma Index is both a stigma-measuring and a community development tool. It recruits HIV-positive people to be community researchers, conducting interviews with other HIV-positive people and asking about every aspect of the experience of stigma.

The Index asks about experiences only over the last year, so that people's memories are fresh and so that later years' results can be compared. Areas covered include:

- Basic demographics, access to health care and medication; reason for HIV testing
- Disclosure to others and their reactions
- Experience of exclusion from family gatherings, religious activities, social groups and so on, or sexual rejection by partners
- Whether people had been gossiped about, harassed, threatened or insulted
- Discrimination: in employment, education, housing and health services
- Self-stigma: feelings of shame, guilt, self-blame, being suicidal etc.
- Self-exclusion: voluntarily opting out or avoiding jobs, social groups, relationships and so on

- Whether people knew that people with HIV were protected by laws such as, in the UK, the Disability Discrimination Act

- Whether the respondent had ever helped another person with HIV, joined a voluntary organisation, or been an HIV campaigner themselves.

Individual countries are allowed to ask supplementary questions; for instance, in the UK, there was a supplementary section on criminalisation of HIV transmission.

The Stigma Index relies entirely on people coming forward. Participants are guided by trained facilitators and fill in the 24-page questionnaire individually. Open-ended discussions and follow-up phone interviews are then used to gather more qualitative data. In the UK 867 people, recruited through community groups, were interviewed.

"More than we were expecting," says the IPPF's Lucy Stackpool-Moore, who has co-ordinated the Index here.

Small pilot studies tested the types of questions in 2006 and last year the Dominican Republic became the first country to conduct a full Stigma Index study, with 1000 people interviewed.

Headline results found that fear of being gossiped about was one of the most all–pervasive fears, but it also found that one in ten people had been assaulted because of their HIV status, and nearly a third of women, usually by their partners. Self-stigma was more common in men than women, with 40% blaming themselves for their own status. Only one in 44 respondents had used the law to combat discrimination, but three-quarters had helped other people with HIV and over a third had confronted or educated people who had stigmatised them. About three-quarters had disclosed to at least one person close to them but in a quarter of these cases they were 'outed' as HIV-positive by a third party.

In 2009 the Stigma Index gained real traction. The UK is one of about 20 countries to have conducted a full study this year, and results will be announced at a launch in the House of Commons on 30 November. Preliminary findings suggest lower levels of gossip, harassment and violence in the UK, but quite high levels of stigmatisation by healthcare workers and educational institutions, and higher levels of self-stigmatisation, shared equally between men and women.

Some previewed quotations from the interviews bring to life these themes:

"When the nurse put on two gloves I was so humiliated, I mean who taught her to do that?"

"I am an asylum seeker and people don't want people who have nothing. I am HIV-positive. If I could get rid of just one of these things…"

Other countries to report around World AIDS Day include China, Thailand and Bangladesh, and the process is underway in the Philippines, Pakistan, Mexico, El Salvador, Columbia, Argentina, Zambia, Kenya, Nigeria, Fiji and Ethiopia.

In the UK the Index was funded by the MAC AIDS Foundation and the Scottish Government; more money will be needed for a detailed analysis and report next year, which will include the stories from participants to bring the data alive.

Are the self-selected Stigma Index interviewees representative of people with HIV?

"Sampling is word of mouth," agrees Stackpool-Moore. "So they had to be linked into some sort of network. But many people had never disclosed to anyone in their family, for instance".

The main aim of the Stigma Index is to establish a baseline for the future. The idea is to repeat the exercise every few years to see how HIV stigma, or people's experience of it, changes. The UK survey is big enough to get some really specific results: "We could see, for instance, if people in London had different issues from people in Manchester, or asylum seekers from gay men," Stackpool-Moore says.

The other aim is to influence policy. Some prevention interventions, for instance, may fail because they are ill-informed about feelings on issues like testing or disclosure.

The Stigma Index won't ascribe a stigma rating to countries. To do so, given the complex nature of stigma, would be impossible.

"We don't want to reduce experience to numbers," says Stackpool-Moore. "But we do want to capture it in the most scientific and quantitative way we can, and to ensure that the experience of people living with HIV informs future developments that are supposed to benefit them." ■

The launch of The People Living with HIV Stigma Index UK report is on 30 November 2009, 3-5pm, Attlee Suite at the House of Commons. Contact ukstigmaindex@ippf.org.
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