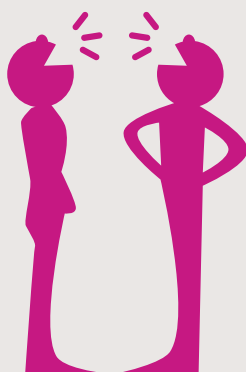
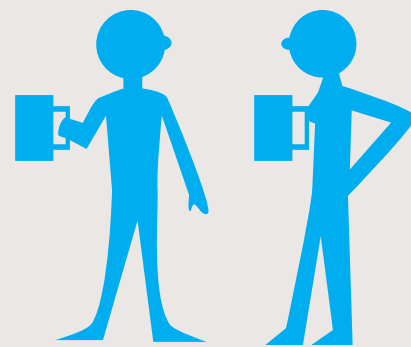
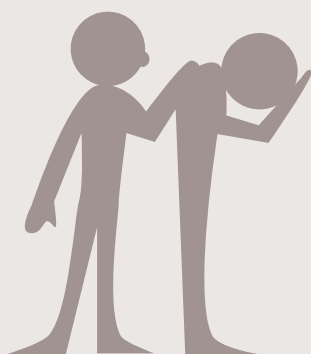


hiv treatment update



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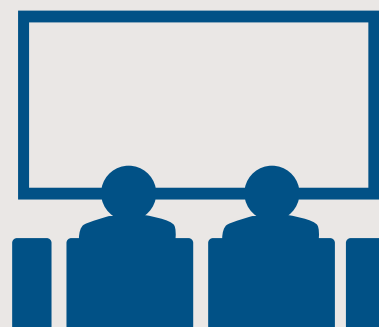
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Gus Cairns

in this issue

We hope, as you read this, that you're about to have a very happy festive season. This is a time traditionally to renew ties with friends and family and, as we find out in this issue, a supportive circle of close friends can have an astonishingly direct effect on your physical health, not to mention your happiness. September's article on positive psychology (*Walking Back to Happiness*, issue 189) was well received, and we offer *The Best of Friends* (page 4) as a seasonal companion.

There's been some good news to accompany World AIDS Day this year. The number of people dying of AIDS in the world has really started to tumble, at a rate of about 10% a year, and the number living with the virus has probably passed its peak too. It's of historic significance that the World Health Organization and UNAIDS are able to celebrate this in their annual World AIDS Day report (see page 12).

No one measure has delivered this. Successful prevention and education initiatives, viral 'burnout' killing off the most vulnerable – and most infectious – people, and increasing availability of antiretroviral drugs have all contributed to reducing the pool of infection and deaths.

This good news, however, is tempered by a lot of 'buts':

HIV is *not* on the decrease in the UK. There are now 83,000 people with HIV here. That's the equivalent of the population of Watford. It works out as one positive person on every A40 Airbus flight, and, in the higher-prevalence area of London, four on every peak-hour tube train. And

because one person with HIV dies for every 14 newly diagnosed, these figures will increase for some time to come.

As Médecins sans Frontières highlights in a recent report (see page 12), the progress we have achieved could be reversed if money for HIV programmes starts to dry up. Global recession, complacency, and resentment that HIV seems to get the lion's share of global health funding could all conspire to throw into reverse the last decade's gains.

As we find out opposite (see *Upfront*), while AIDS in its classic form may become a rarity amongst everyone but those diagnosed late, the positive population, especially as they age, may continue to have complex medical needs. We may be more prone to conditions ranging from heart attacks and cancer to dementia and, as we find out on page 14, sleep disorders.

That implies we may have a fight on our hands in the developed world as well as in the global South to ensure that people with HIV get the healthcare resources they need.

While we may have corralled the 'untamed beast' that is HIV, we haven't found a way to kill or permanently tame it, as Keith Alcorn reminds us on page 8. Until we can come up with better ways to prevent HIV infection and render infections harmless, we will continue to be reliant on an expensive and lifelong programme of drugs.

A cure for HIV: that really would be a Christmas present worth celebrating.



hiv treatment update

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Why we won't die of AIDS

A study in France has found that, whatever older people with HIV die of, it probably won't be AIDS.

In recent years one of the increasingly hot topics in the HIV community has been the realisation that people with HIV are living into older age – and that this means they will start developing the health conditions of older people.

At the recent European AIDS Conference in Cologne, a new set of European HIV treatment guidelines was presented.¹ We'll look at them in detail in the next issue. But what was interesting was that, while the guidelines for HIV treatment changed very little, a big new section was added on managing all sorts of other conditions.

Diabetes, liver disease, high blood pressure, depression, osteoporosis – most of them common conditions that affect the general population, and most of which become significant as we age.

Antiretroviral therapy works and is simpler and more potent than ever. Yes, not everyone is ready to take it or needs it. Yes, there are still side-effects and some of these may intensify or even set off certain conditions.

But in future, the tricky medical issues in HIV medicine will be, for most patients, about everything *but* antiretroviral (ARV) treatment. The guidelines suggest that in the future, for most of us, our dodgy tickers and our brittle bones are likely to matter more than our CD4 count.

There was a fascinating study presented at the conference that backed this up.

A study of 149 people with HIV aged over 60 found that over a four-year period more of them died than would have been expected in the general population – but

not a single person died of an AIDS-defining condition.²

Most studies of people with HIV have taken 50 as the threshold of older age, but in this French study all patients were over 60, the average age was 65, and nearly 10% were over 80 (the oldest was 86). Starting an 'ageing cohort' at 60 may give a more reliable guide to the diseases we may have to look out for as we age.

Between 2004 and 2008, 21 of these patients died. This 14% mortality rate is higher than in the general population, but it's not *vastly* higher. For instance, the four-year mortality rate in men aged 70 in the UK is 11.1% and in women 7.1%.³ (In France, which has a better life expectancy than the UK, it would be slightly lower.)

The most striking finding of the study was that not a single patient in the group developed a new AIDS-defining condition over the four years, and only two experienced the relapse of an existing condition (Kaposi's sarcoma and lymphoma). This is despite the fact that one-third had had an AIDS diagnosis in the past.

Test results also bore witness to the success of ARV therapy. In 2004, 70% of the group had a viral load under 50 copies/ml; by 2008 this had increased to 96%. Average CD4 counts increased from 372 to 494 cells/mm³ in the same period.

So what did the 21 patients die of? Eleven deaths, more than 50%, were due to non-AIDS defining cancers. Another four (19%) died of cardiovascular disease (CVD), three (14%) of liver disease, and three of other causes including one of dementia.

Many of those still living had multiple health problems. Even though CVD was not the main cause of death, it was by far the most common cause of illness. Half the group (74

patients) suffered from a CVD-related 'event' such as a heart attack, angina or a stroke during the four years. This may indicate that CVD will become a more important cause of death as the cohort ages.

A quarter of the patients had kidney disease, one in five had arthritis or bone problems, one in six had cognitive or neurological problems, more than one in seven had diabetes, and one in eleven had liver problems.

One in six (15 patients) also currently had some form of non-AIDS-defining cancer. These high rates of cancer are of concern. Last month's piece on how HIV causes AIDS (*How does HIV make us sick?* issue 191) found evidence that, despite HIV therapy, chronic HIV infection leaves 'gaps' in the immune system, and that HIV may continue to smoulder, causing a low-key version of the inflammation that is thought to lie behind CD4 depletion.

In patients on ARVs it does not cause this, but may continue to damage nerve cells and the linings of arteries, and it may damage the immune machinery that nips cancers in the bud.

What this means is, while we may have – to a large extent – won the fight against classic AIDS, there is an awful lot of HIV research still to be done before we can all expect to live as long as anyone else.

50 Plus

Are you over 50 and living with HIV in the UK? If so, the Terrence Higgins Trust, Help the Aged and Age Concern want to hear about your views and needs in their online survey, running until January 4th. For more information visit www.tht.org.uk/howyoucanhelpus/surveys

the best of friends



Gus Cairns explores how friends can be good (and sometimes bad) for your health

Recently we've been hearing a lot about swine flu, and how you should stay at home if you've got it. Makes sense: after all, these viruses are spread by contact. So if you keep in close proximity to others, you're more likely to get sick, aren't you?

Friends and colds

Not if a pioneering study conducted in the late 1990s in Pittsburgh, USA holds as true for flu as it does for that other air-borne misery, the common cold.¹ It found that, on the contrary, the fewer social contacts people had, and the smaller the variety of their social contacts, the more likely they were to suffer from colds. Not to become infected – but to become ill once they were infected. The greater number and variety of friends people had, the less likely they were to develop cold symptoms.

It was a strong effect: people with the fewest social contacts were four times more likely than the most sociable people to get streaming colds if infected. The absolute number of contacts people had was not as important as the number of *types* of contacts people had.

In the study, 276 people aged 18 to 55 had a health screen, risk factors like smoking and stress were evaluated and a psychological screen gauged their personality type.

They were asked to number the people they'd had social contact with, in person or by phone, in the last two weeks and to divide these into categories including spouse, family, close friends, workmates,

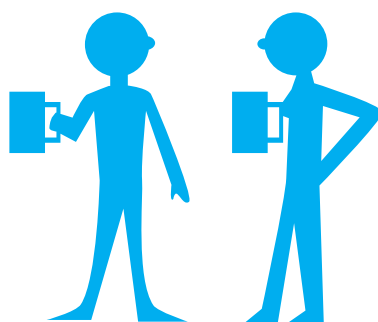
neighbours and members of social groups. They were exposed to cold viruses and then kept in quarantine while their cold symptoms were assessed by objective criteria, which included collecting and weighing their soggy tissues for 'mucous production'.

Sociability was the strongest predictor of cold symptoms. Compared with the most sociable people, the least sociable people produced more mucous and their nasal passages were less efficient at getting rid of it.

The researchers found one chemical difference between the social and the non-social people: the latter had higher levels of adrenaline and noradrenaline – they were more stressed. Friends, in short, are good for your immune system.

All very well, but is friendship able to influence potentially lethal illnesses to the same extent as it can a relatively trivial illness like a cold?

Very much so. Numerous studies have found that the number and variety of friends people have, has a directly positive effect on health outcomes.



A study of women with breast cancer, for instance,² found that a higher number of supportive friends, more contact with them and a larger social network independently predicted better survival rates, and the effect was nearly as strong a predictor of survival as the stage the cancer had reached when detected.

Another medical outcome strongly affected by social ties is the chance of having a second heart attack after you've had a first. A review of various studies³ found that people with a good social network had better heart functioning and a longer period between the first and any subsequent cardiovascular event. This wasn't just because friends remind you to eat well, sleep well and stress less (though the influence of friends on behaviour is very important, as we'll see below): having good social contacts appeared to have a directly beneficial effect on immune functioning and heart function.

Finally, it's been known for 30 years that friendship, or lack of it, has a direct effect on mortality: a long-standing study of 6928 adults in California⁴ found that, regardless of age, men who lacked social and community ties were 2.3 times more likely, and women 2.8 times more likely, to die during the study period.

Loneliness and HIV

Being diagnosed, and living, with HIV can be a significant cause of social isolation. Loneliness can be caused by stigma and rejection, fear of stigma and self-isolation, and, especially in the earlier days of the epidemic and still in some

settings, by having to deal with multiple bereavement, caring for the dying, and facing one's own possible death.

Early studies certainly found a correlation between social isolation and factors like the speed of CD4 count decline. A 1993 study, for instance,⁵ found that people with HIV infection, largely symptomatic, had faster CD4 declines if they had poorer social support.

Loneliness is also predictive of poor adherence. A 2004 study of 90 people with HIV found that greater social support related to better adherence, whereas higher depression scores related to non-adherence.⁶ Having friends didn't, it seemed, work directly to improve adherence in the sense of friends reminding each other to take their meds, but produced a positive state of mind in which people were more committed to their own health.



Friendship has also been studied in HIV prevention, where studies have experimented with training-up influential people in existing social networks to act as peer-group safer-sex advocates. This 'popular opinion leader' concept has had its greatest successes among groups who are marginalised and where there is a corresponding sense of community solidarity, for instance young gay black men in the USA and young Roma (gypsy) men in eastern Europe. It works less well in situations where social bonds are not already strong.

An insight into how marginalisation can be overcome to create a healthier lifestyle comes from a survey of 154 young gay Asian men in New York.⁷ It found that, while experiences of homophobia and racism were associated with higher levels of sexual risk-taking, talking to gay friends about this discrimination was associated with lower



I found support groups and I found dating websites. But there was nothing in between.

Michael Patel,
Founder of PlusFriends

levels of risk. It appears that men who didn't have friends to talk to were more likely to blame themselves, both for being gay and for risky sexual encounters.

The PlusFriends group

Diagnosis can still feel like a lonely time even if you have a good circle of friends. Michael Patel was diagnosed at the age of 36 in 2005.

"I had a good social life and a lot of wonderful friends, but not one of them had HIV," he says. "I didn't feel I had to explain it to them, but they would say things like 'I understand what you're going through' and I'd be thinking 'You really don't'."

He went to a support group for newly diagnosed gay men, but didn't enjoy the experience.

"I hated it. Support groups are very good and help a lot of people but they aren't for me, and I suspect aren't for a lot of people. It took me three weeks to say anything and I hated the way that in a support group you feel a kind of spotlight turning to you and you *have* to say something.

"Now, I'm the sort of person who's learned to do things by myself, to 'pick myself up, dust myself off, start all over again'. I'm too proud to break down in public, in a support group where initially nobody knows anybody. I did make friends via the support group, but in terms of what it actually did, I'd leave feeling really bad about myself – worse than when I came in."

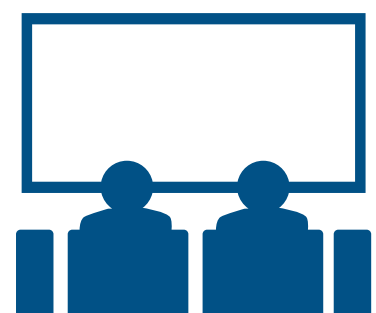
And yet, he says, he knew he badly needed support and the right kind of opportunity to talk. What he needed, in short, was an understanding friend who had HIV themselves and somewhere to meet one.

"I Googled, I searched, I couldn't find a social group for HIV-positive people anywhere. I found support groups and I found dating websites. But there was nothing in between."

So he found an existing internet structure – the Meetup website, through which people with a similar interest can arrange social events – and formed the London Gay HIV Meetup Group. Which soon became, when he realised the 'HIV' was putting people off, PlusFriends.

At one time, I went to a few PlusFriends meetings. Why? I'd had HIV for 18 years and if all the counselling and workshops I'd had to explore my issues about HIV hadn't worked yet, they weren't going to. I wanted to socialise, and maybe date, in an atmosphere that wasn't all about sex. And I didn't want to disclose every time or spend the evening educating someone about HIV. Meetings ranged from a boozy outing watching the Rugby World Cup to dinner in a fancy restaurant.

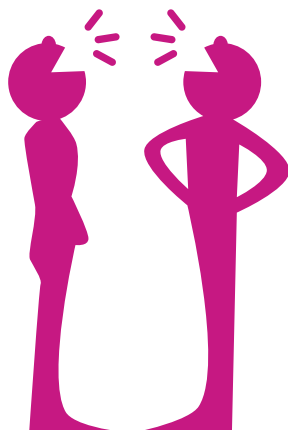
The PlusFriends group now has about 350 members, though some are just internet buddies and only 15 to 20 people may come along to any one event. A core group meets fairly



regularly and has regular activities such as a Sunday lunch or Saturday brunch, which often turns into an afternoon of museums, shopping and a disco night. For fans of healthier activities, there are regular walks.

“If you meet in a pub, there’s not the pressure to talk,” says Michael, “and there’s the opportunity to do it your way, at your own pace, in a one-to-one setting. With guys who are very nervous, I encourage them to meet with one other group member first and then come along.”

People come along for a variety of different motives. “There are guys who have been HIV-positive for a long time and would ideally like to find a partner who also has HIV. There are some older members who come along and make it their job to welcome others. There’s newly diagnosed guys who need to talk but don’t like support groups. And there’s guys who probably *should* go to support groups – I’ve had to shepherd home a few who were so nervous they drank too much.” Michael, an accountant by trade, says that, ironically, running the group has got him interested in training as a counsellor.



The bathing beauties

Gay men, of course, are not the only people with HIV who may want to make HIV-positive friends. One of the incidents that prompted this article was an outing I had with a sociable female friend of mine, of equally long diagnosis, and her friends, none of whom had HIV. We had a nice dinner but afterwards, almost inevitably, ended up chatting to each other in a corner about pills, doctors and CD4s. “It’s such a *relief* at times to talk to someone and not have to explain all this,” she said.



The bathing beauties at the ladies’ pond: (l-r) Leigh, Silvia, Babs, Clair and Carolyn.



“So how do HIV-positive people who have outgrown support groups socialise?” asks Angelina Namiba of Positively Women.

“In the beginning,” she says, “especially when someone is newly diagnosed, support groups are not only a source of much-needed support and information. They are a place for networking and socialising too, especially for many who have not disclosed their status. Support groups may be the only place that helps them overcome the isolation they may face and many friendships are born out of accessing support groups.

“Amongst the many I now consider my very good friends, are women I have met over the years in various support groups and through the course of my work.

“But,” she adds, “many of us positive dinosaurs who have been diagnosed for a few years now have outgrown support groups.



“So what do we do for fun? Ours is an informal group of positive women with a combined total of over 100 positive years! We go salsa dancing...some of us go to the theatre now and again as well as go to lots of the free jazz events around London in the summer.

“Earlier on this summer, one of our group, Julia, came up with the idea of a picnic...at Hampstead Heath. A number of us even braved the cold water of the ladies’ pond! It was great. There were six of us altogether. Everyone brought a dish and a drink to share. It’s something we will certainly be doing again come next summer!”

United we fall – when friends are bad for you

So: friendship and socialising are good for your mental and physical health?

Not always. Like everything in life, the picture is more complex than that. Sometimes friends get each other into bad habits.

One study in the late 1990s⁸ found that, contrary to expectation, among 205 HIV-positive men, *lower* levels of loneliness predicted more rapid declines in CD4 counts. These CD4 declines did not seem to have anything to do with medication adherence or sexual practices. Significantly, they also were not correlated with negative emotions.

An exception to the rule? No. A review of other studies of friendship and social support⁹ by the same authors found that, quite consistently, people who perceived themselves as having stronger links to friendship networks actually progressed faster to AIDS – if they were asymptomatic. Once they became sick, however, the opposite happened: supportive friends produced better health outcomes and survival.

People don't seek friends in order to have a healthier lifestyle: they seek friendship because it makes them happier. But if those friends are doing things that are bad for your health, this can have the paradoxical effect that social integration can make you ill. The authors found that strong friendship networks tended to expose people to more temptation: they were more likely to take part in high-risk sexual behaviour and "socially facilitated health-compromising behaviour" such as drink and drugs.



Social ties don't always help in prevention either. This was noticed in a study of a gay men's prevention intervention that reported in 2004.¹⁰ Peer-led workshops in San Francisco and New York were designed to get gay men talking about the sexual risks they'd been taking and think of ways of reducing the risk. Overall, the intervention did not produce a significant reduction in unsafe sex, to the researchers' disappointment. When they investigated why, they found that the lower-risk gay men were tending to adopt the sexual practices of the higher-risk men. Peer group influences were working – but in the wrong way.

The way this works has been demonstrated in an extraordinary series of studies by Nicholas Christakis and James Fowler of the Harvard School of Public Health. The town of Framingham, Massachusetts, has given its name to a



measure of heart attack risk – your Framingham score – because a huge scientific study has been ongoing since 1948, quantifying the risks associated with heart attacks in three generations of New Englanders.

The original records of the study included the details of study participants' close friends, colleagues and family members, compiled so that people who dropped out of the study could be traced. This allowed Christakis and Fowler not only to see if social integration predicted health behaviours, but also to see how members of the social network influenced each other over time. If one person in a closely connected group changed their behaviour, would others follow? How fast did a health behaviour spread through a network?

They investigated a troubling behavioural epidemic that has taken hold in the last few decades, and threatens the health of people worldwide – obesity.¹¹ They found that in 1948, 10% of the Framingham study group was obese. In 1985, 18% of the 12,067 people they investigated were obese; but the rate accelerated fiercely and by 2005 40% of the population was obese.

Christakis and Fowler found that obesity spread as if it was a virus, radiating out from individuals. Clusters of people would become obese at the same time, and the closer you were to someone who was obese, the more likely you were to become obese yourself.

But for the purposes of this article, the most striking finding is that the most 'infectious' people were close friends. Having an obese spouse increased your chances of becoming obese by 37%, but having an obese friend increased the risk by 60%.

This 'infection rate' ensured that thin people whose friends were obese soon became very rare, and that obese people tended to be the most well-connected; there were two large, closely connected

networks of predominantly obese people in the centre of the social network, and a lot of thin loners on the outside. Doesn't this sound like the studies of closely related genetic 'clusters' of HIV in high-risk communities?

This all seemed to be related to social norms of diet and physical appearance. Interviewed in *Wired* magazine earlier this year, Nicholas Christakis said: "A bunch of people discovered fast food at the same time. Then the network took over."

Not smoking and smiling – both are infectious

Luckily, this means that if a healthy behaviour becomes accepted as a social norm, then friendship networks can have a reinforcing effect. Christakis and Fowler found that giving up smoking spread like a virus too.¹² In 1971, 65% of the Framingham cohort smoked – higher than average, even for the time. By 2001 that was down to the national average of 25%. The 'infection rate' of a friend giving up smoking was 36% above what you'd expect if stopping smoking was random. Here, however, the influence of a spouse was stronger at 67%. Smokers did not give up one by one – characteristically, a whole group would give up at once.

Christakis told the *New York Times*: "It's not like one little star turning off at a time," he said. "Whole constellations are blinking off at once."

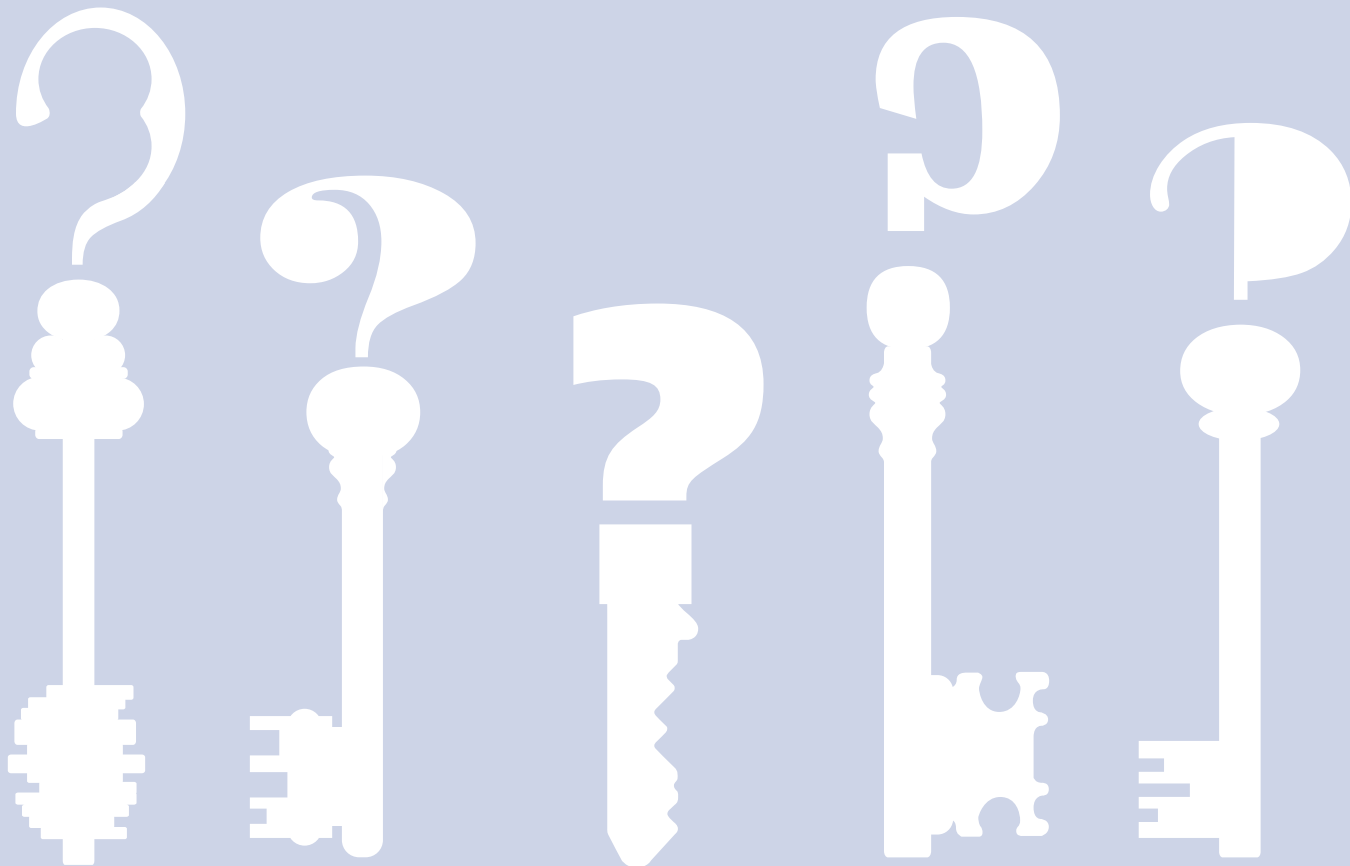
And yes, happiness is infectious too. The Framingham participants rated their mood in psychological questionnaires over decades.¹³ It found that unhappy people surrounded by happy people soon stopped being unhappy. Who were the most efficient transmitters of happiness? Not spouses, whose 'happiness infection rate' was only 8%, but friends. A mutual friend's infection rate was 25%, and if they lived nearby, that rate skyrocketed to 65%.

Friends may not always make us well: but they are amongst the strongest causes of happiness. ■

● **Plus Friends Group:** see www.meetup.com/plusfriends

● **Positively Women:** see www.positivelywomen.org.uk

the cure



Could we eliminate HIV from the body altogether? *Keith Alcorn* looks at the latest milestones in a long journey of discovery.

Back in 1996, when highly active antiretroviral therapy (HAART) began to transform HIV care, there was much talk of its potential to eradicate HIV from the body altogether, which would amount to a cure.

I remember a standing-room-only talk where combination therapy pioneer, Dr David Ho, explained to the Vancouver International AIDS Conference how the new viral load test could measure the decline in virus levels in newly infected patients treated with HAART. The two-phase decline would probably last from one to four months, until all the cells presumed to harbour HIV had died off.

Eradication looked entirely feasible from the optimistic viewpoint of 1996.

Little more than a year later, doubts began to accumulate. HIV was found to infect a group of longer-lived immune system cells called memory CD4 lymphocytes. By late 1999, scientists had concluded that it would take at least 60 years for this group of cells to die out. The idea of cure disappeared from the conference circuit.

Nonetheless, knowledge about the mechanisms that allow HIV to persist in the human body continued to accumulate. A number of tenacious scientists are still probing the reservoir

of HIV-infected cells and learning more about how the virus can lurk silently within the genetic code of a few thousand human cells, ready to spark an explosion of viral replication if HAART ceases.

Suddenly, in 2008, scientists began discussing the subject with more enthusiasm. The field was partly stimulated into action by excitement over the apparent potency of the new integrase inhibitor raltegravir (*Isentress*), and a belief that its ability to clear virus more rapidly than other drugs might portend some greater capacity to penetrate into places other drugs could not reach. It was also

nurtured by funding from the American Foundation for AIDS Research (amfAR), which never lost faith in the possibility of a cure for HIV.

Last November I attended a meeting in Washington where 40 scientists, convened by amfAR and the Treatment Action Group, sat down to thrash out the key scientific questions about how to cure HIV infection. A sign of the change in the scientific weather was a ten-minute appearance by Dr Anthony Fauci, the director of the US National Institute of Allergy and Infectious Diseases, an organisation with a budget of \$4.7 billion to spend in 2009. Fauci's appearance signalled that research into a cure was now being taken more seriously.

More research on possible ways of curing HIV infection was published this year alone than in the whole of the previous decade. In March a group of US researchers published a call for a global public-private partnership to accelerate research into a cure, and called on the US National Institutes of Health – the main funding body for medical research in the US – to devote long-term funding to the goal.

Why are scientists suddenly so interested, and what are the realistic prospects of a cure?

The Berlin patient

A key development which has got people talking about a cure again is the report of an apparent cure in a Berlin man who underwent a bone marrow transplant for treatment of leukaemia while also receiving antiretroviral drugs (ARVs).¹ The man received bone marrow from a donor who had natural resistance to HIV infection; this was due to a genetic profile which led to the CCR5 co-receptor being absent from his cells. The most common variety of HIV uses CCR5 as its 'docking station', attaching to it in order to enter and infect CD4 cells, and people with this mutation are almost completely protected against infection.

More than two years after two bone marrow transplants (the first failed), the man remained free of HIV as far as the most sensitive tests could determine. Although the researchers who reported the case decline to describe it as

More research on possible ways of curing HIV infection was published in 2009 alone than in the whole of the previous decade.

eradication of HIV, the results are intriguing.

However, the mechanism that has led to this long-term halt in viral replication (we'll come to definitions of a cure later) is still unclear.

In bone marrow transplants the patient's population of cancerous immune cells is destroyed and then the immune system repopulated by stem cells from the donor's bone marrow. Did this eliminate HIV? Unlikely, because there have been previous cases of viral resurgence in people who received transplants.

Was it because the stem cells lacked the CCR5 receptor, leaving HIV no opportunity to enter new cells and replicate? Possibly, but most people have some viruses which are able to use other receptors, and in this patient, a tiny number were present before the transplant. Furthermore, some immune cells *with* CCR5 receptors were still present in the patient's gut six months after transplantation.

Was it the use of immunosuppressive drugs after the transplant, which would stop HIV-infected cells 'waking up'? It's impossible to tell, although the key drug used (cyclosporine) has been tested as an adjunct to HAART to limit the number of target cells the virus might infect.

Despite these unanswered questions, researchers believe that the findings

suggest a role for suppressing the production of CCR5-bearing cells, either through such transplants, or by gene therapy.

Scientists were sufficiently intrigued that they met in Berlin earlier this year to discuss how they could co-ordinate efforts to identify CCR5-lacking donors and expand the supply of stem cells from them, for example through sampling blood cells from the umbilical cord of babies born to mothers who have the mutation, in order to eventually facilitate stem-cell therapy.²

Gene therapy techniques which can transform stem cells – and all their descendents – into cells resistant to HIV entry may be a more practical option than looking for matching donors. Several US research groups announced in late October that they had received funding to explore techniques for engineering and introducing CCR5-deficient stem cells. If these approaches prove successful they will be expensive, so in the early stages it is likely that they would be reserved for people with no remaining treatment options or a cancer requiring bone marrow or stem cell transfer. But given that the lifetime cost of treating someone with HIV with ARVs is close to £200,000 if they live for at least 35 years after diagnosis,³ these techniques may become more cost-effective in time.

Other researchers are beginning to think in terms of combinations of drug therapies and immunological therapies that can rid the body of HIV-infected cells.

Challenge one – bringing HIV out of hiding

HIV infection is currently impossible to cure because when the virus infects an immune system cell, its genetic material becomes integrated into the human DNA in the cell. If the cell is activated to respond to an infection, it begins pumping out new viruses. These infect other activated cells in the vicinity, and the same cycle begins all over again.

As we have said, a population of HIV-infected cells persists in the body, ready to begin producing HIV when the viral sequence within it becomes activated. In these latently infected cells HIV is tucked away in a section of the genome

not activated by normal cellular processes, rather like a moth chrysalis secreted in the corner of a cupboard, invisible to the naked eye. Only when it receives a specific chemical signal will it emerge.

Such latent virus is invisible to the immune system and therefore impossible to eradicate. But latency might be overcome by giving immune system cells a massive shock, causing them to pump out virus which can then be cleared by antiretroviral drugs, and so permanently reducing the number of infected cells.

This is a potentially risky strategy. The consequences of activating all the cells of the immune system potentially infected with HIV might be catastrophic, as researchers found in a recent trial of a drug being developed to treat rheumatoid arthritis. Intended to modestly stimulate CD4 memory cells, it had such an overstimulating effect that six men suffered severe organ damage.

Studies have looked at several immune activation approaches in combination with HAART, but no study so far has demonstrated long-term reductions in the amount of cells containing HIV DNA.

Latent sequences are kept tucked up within neatly wrapped bundles of DNA, like cotton round a spool. The 'spools' are proteins called histones, and the DNA – with its secret payload of viral genes – can be kept from producing new proteins by the presence of enzymes called histone deacetylases (HDACs).

A number of research groups have been investigating HDAC inhibitors, which would allow the spools to uncoil, as a means of switching on HIV and making it a target for destruction, and several drug companies are beginning to take an interest in this area.

An Italian research group used HDAC inhibitors in combination with a substance that would lower levels of the protective antioxidant glutathione in latently infected cells. This stresses the cell into greater HIV transcription when HDAC inhibition takes place. The stressed cell eventually self-destructs. The researchers dubbed the process, which has been tested so far only in the laboratory, 'shock and kill'.⁴

We have reached the theoretical limit of antiretroviral therapy.

Robert Siliciano, Johns Hopkins University

HDACs regulate many vital cellular processes, and interfering with them could produce long-term side-effects unless the compounds chosen are highly specific for the HDACs involved in controlling HIV latency. For this reason, products already in use for other diseases, such as cancers, are likely to be tested in humans with HIV before novel products are used. A group from the University of Carolina recently reported that not all HDAC inhibitors stimulated viral replication to the same extent and we will need ones that maximise viral transcription while minimising toxicity.

Robert Siliciano of Johns Hopkins University and colleagues recently announced that they have developed a fast-throughput means of screening compounds to identify agents that can activate latent HIV without activating the CD4 cell.

Challenge two: finding the hiding places

Another key challenge is finding out where all these latently infected cells are hiding.

Intensifying treatment with new classes of drugs like integrase inhibitors has not proved capable of further reducing the very low levels of virus seen in people on HAART, suggesting that the virus is being released from places not affected by HAART – the so-called 'reservoirs'.^{5,6}

Robert Siliciano tested patients using ultrasensitive assays and has found that most people with a viral load below 50

copies/ml still have some detectable viral replication.

"We have reached the theoretical limit of antiretroviral therapy," he said at the 16th Conference on Retroviruses and Opportunistic Infections this year.

Any residual virus detected in a fully adherent person on HAART – including viral blips when levels can rise above 50 copies/ml – appears to be coming from latently infected cells in a reservoir that is invulnerable to HAART. One of these may be HIV-infected cells in the gut, which CD4 cells come into contact with during their normal trafficking around the body.

HIV infects cells in the lymphoid tissues, which are marshalling yards where foreign matter is presented to the immune system for inspection. Lymph nodes, which are full of CD4 cells, are distributed all around the body, and rapidly become packed with HIV after infection. However, the greatest concentration of cells infected with HIV lies in the abundant lymphoid tissue in the walls of the gut, which is the main route for foreign matter entering the body.

There is also speculation that the virus infects cells in the bone marrow that eventually differentiate into various immune system cells. Every time the cell divides, it takes with it a copy of the instructions for making HIV.⁷ This is certainly what happens after HIV infects memory CD4 cells, which retain information about previously encountered infections so that they can quickly respond if it is encountered again. These cells replicate more frequently as the CD4 count falls, perhaps explaining why the reservoir of HIV-infected cells is so much larger in people with chronic HIV infection.⁸

The reservoirs become established in the first weeks of infection, before replication is checked by the partially successful response of the immune system. However, the size of the reservoir is strongly influenced by the duration of unchecked viral replication and the severity of CD4 decline.⁹

Experiments by Anthony Fauci's research group indicate that in a person who has received fully suppressive HAART for several years, the reservoir

varies from one infected CD4 cell in every billion in people treated soon after infection, to one infected cell in every 10,000 CD4 cells in people who began treatment when chronically infected.

In almost all people who started HAART less than six months after infection, infectious virus could no longer be cultured from their cells after one year of treatment whereas it was still detectable in everyone who started treatment later, despite three to six years of HAART.¹⁰

“Antiretroviral therapy probably completely stops the entry of newly infected cells into this pool [the reservoir]. Our job is to make the exit of cells from this pool quicker, in a way that’s clinically practical and safe,” says Professor David Margolis of the University of North Carolina.

In people with good immune reconstitution, most of the integrated HIV genes are found in central memory cells. Clearing the reservoirs will require the elimination of these cells, in a very targeted way instead of blasting the immune system away with crude chemotherapy.

Challenge three – understanding how eradication happens

It will be challenging to test for residual virus, especially latent, replication-competent virus, and to be able to measure what’s going on when drugs are used against it.

Describing experiments to clear latently infected cells, David Margolis says that currently, “we’re doing something at one end [putting in drugs] and measuring something at the other end [observing changes in viral load and the number of infected cells], and what’s in between is a black box.”

What’s not clear is whether all latently infected cells are the same. Some researchers suggest that latently infected cells have a variety of behaviours, requiring a variety of drug targeting methods, and that some may be permanently stuck in a resting state, unlikely to be activated. In addition, some of the HIV genetic material is just junk – ‘replication incompetent’. But determining what’s what will require

years of work to examine the latently infected cells.

The road ahead

The best chance of eradication, most experts agree, is likely to be in people who can be treated within weeks of becoming infected, before the reservoirs have a chance to become well-established.

In this patient group, Professor Routy suggests, we could use CCR5 inhibitors to limit the number of cells the virus enters, integrase inhibitors to prevent it installing its genes in the DNA of cells it does enter, and the cytokine interleukin-7 to activate cells that are infected in order to mobilise lymphocytes to kill cells that are producing HIV.

In people with chronic infection the biggest challenge is the size of the reservoir of infected cells. If that could be at least reduced, viral replication might be held at bay by immune responses.

Immune responses could be strengthened by therapeutic vaccination. The idea of therapeutic vaccination is to enhance the body’s own immune response to HIV by finding ways to hyper-sensitise parts of the immune system to viral components, with the intention of inducing an immune state that can keep viral load low without drugs, thereby prolonging the time that can be spent off HAART.

So far, though, this approach has produced little in the way of immune control of HIV, with the exception of preliminary results from a recent Canadian study which suggested that a vaccine tailored for each individual in the study appeared to keep HIV below pre-treatment levels during a 12-week treatment interruption.¹¹ The ultimate aim of a therapeutic vaccine is to ensure that the viral load remains undetectable and that the cytotoxic T-cells, or CD8 cells, recognise and kill any infected cell that is on the verge of spewing out virus. Clearly there’s a long way to go.

The alternative is to look for strategies that can sustain latency, by further protecting HIV from activation and by exquisite targeting of latently infected cells. However, this is no more than a concept at present, with no hard

evidence to show whether compounds already exist that can reinforce the latent state or induce a permanently ‘stuck’ state in the cells infected with HIV, rendering them unable to be activated and thus incapable of producing HIV with the ability to infect new target cells.

What sort of cure might be possible?

The preferred outcome must be complete eradication – a treatment programme that results in elimination of all traces of HIV from the body. This may prove very difficult.

A more plausible outcome is remission, the lack of detectable virus in the absence of treatment. Given the difficulty of finding and measuring HIV in latently infected cells, this may be the best that can be achieved.

In hepatitis C, cure is defined as a sustained virological response to treatment – no detectable hepatitis C viral RNA in the blood six months after treatment ends. However, there is evidence that very low levels of replication-competent hepatitis C viruses can persist in the blood for up to five years after successful treatment. Because hepatitis C does not become part of our own cells’ genes, it is easier to imagine eventually deleting every single bit of virus in the body.

Such data show how difficult the idea of eradicating HIV is, but do suggest that a treatment that mobilises the natural immune response to viral infection – alpha-interferon in the case of hepatitis C – may be crucial if infection is to be cured.

Even inducing an immune state that completely suppressed viral replication might not be enough. What if persistent viral replication continues in the brain, a ‘sanctuary site’ that drugs and the immune system may not completely be able to reach? And what if age-related loss of immunity eventually undermines remission?

For all these reasons, our ultimate goal may still need to be the elimination from the body of every cell containing potentially reproducible HIV. Research so far has indicated which roads might reach this goal, but travelling along them will be a long journey. ■

news in brief



HIV worldwide

HIV treatment brings down deaths worldwide

The increasing availability of HIV treatment is paying dividends, according to the annual report on the state of the global HIV epidemic released by UNAIDS and the World Health Organization.¹

Despite this, the international charity Médecins sans Frontières (MSF) warned in a separate report² that financial and political pressures were threatening HIV funding and progress towards greater HIV treatment coverage could not be assumed.

The UNAIDS report says that treatment provision and prevention programmes led to a 10% decline in HIV deaths in 2008. Prevention programmes have also led to a 17% decrease, relative to 2001, in the number of people infected annually. Where these declines have been sustained for some years, AIDS deaths have fallen dramatically: in Botswana AIDS-related deaths fell by 50% between 2003 and 2008.

Four million people were taking antiretrovirals worldwide at the end of 2008, an increase of one million on the year before.

However, more remains to be done and MSF warned that there were worrying signs the momentum might not be sustained.

For every HIV infection stopped by prevention programmes, the report calculates, five infections still happen. And some countries with long-standing HIV programmes still cannot provide anything like universal coverage: for instance only half the Ugandans who need HIV therapy get it.

There are signs that global funding for HIV treatment might be stalling.

Whereas 2008 saw a huge expansion in the money granted by the Global Fund to Fight HIV, Tuberculosis and Malaria, 2009 will see a 35% decrease relative to the previous year. And PEPFAR funding announced by Barack Obama in May 2009 provided no increase on the previous year's grant, with a smaller proportion earmarked for treatment.

HIV & TB

Eastern Europe is world blackspot for TB/HIV

Eastern Europe and Central Asia are the only parts of the world where HIV infections are still increasing, according to the UNAIDS 2009 report (see above). The proportion of their populations infected by HIV has risen by two-thirds since 2001, and Russia and Ukraine have particularly severe epidemics.

Another report¹ finds that patients with tuberculosis (TB) and HIV in this region have higher mortality and are more likely to have multidrug-resistant TB (MDR-TB) than anywhere else in the world.

TB has an extremely high mortality rate in eastern Europe. The report found that a year after diagnosis, only one in 20 patients in western Europe had died, but one in four in the east.

The reasons were to do with the failure of both TB and HIV therapy. TB was cured in 85% of patients in the west but only 48% in the east, and HIV therapy was only started by 30% of patients in the east compared with over three-quarters of patients in the west.

Resistance to key TB drugs was also much more common. In Russia, for instance, 13% of all new TB cases are of MDR-TB, compared with 0.7% in the UK.

The authors of an accompanying editorial said that MDR-TB posed a threat to the global population.

HIV treatment

Protease inhibitor monotherapy: is it viable?

A session at the recent European AIDS Conference was devoted to studies of protease inhibitor monotherapy – using one drug (boosted by a second, ritonavir) as a complete HIV therapy in itself. Will this be sufficient to suppress HIV?

While there were pretty convincing data from one study, other studies still posed questions around the long-term viability of the approach.

The most convincing results were from the largest trial, MONET, a study of darunavir monotherapy in people who had been on successful ARV therapy for at least six months before switching to boosted darunavir.¹ In this study, after nearly a year, 86% of people on darunavir monotherapy had a viral load under 50 copies/ml compared with 88% on combination therapy – not a statistically significant difference.

One reason to put people on monotherapy is to save money. A study comparing drug prices in Germany found that monotherapy was 44% cheaper than standard combination therapy.²

Ritonavir-boosted lopinavir (*Kaletra*) was the first drug used for monotherapy and a study³ from Argentina and Mexico found that after 48 weeks 94% of people on combination therapy and 95% on lopinavir had viral loads below 50 copies/ml. However, in this study if people had viral load 'blips' they were given nucleoside (NRTI) drugs and this was not counted as treatment failure – if it had been, the actual success rate of monotherapy would have been 85%.

A Spanish study⁴ of atazanavir as monotherapy looked less convincing. This study did not have a combination-therapy control group, so it is impossible

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Eastern Europe is world blackspot for TB/HIV

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to say if this would have been more effective, but at 48 weeks 79% of patients had a viral load under 400 copies/ml and only 73% had had more than one viral load reading over 50 copies/ml. Two people who experienced virological failure had developed atazanavir resistance.

Hepatitis C

Hepatitis C probably not spread by semen

German researchers comparing risk behaviours in HIV-positive gay men with and without hepatitis C (HCV) have concluded that HCV is unlikely to be spread through semen. Exposure to blood and rectal trauma is probably necessary to transmit the virus, they conclude.

Exactly how HCV is being spread between HIV-positive men matters, because it informs prevention messages. Some studies have found an association with unprotected sex in general and not only with specific activities that may cause bleeding like fisting, or sharing drug straws.

However, the German study¹ concluded that the only significant risk factors that remained after statistical analysis were receptive fisting without gloves, rectal bleeding, and the use of drugs during group sex. They suggest that some of the confusion about HCV transmission may have arisen because an uninfected person may, as an insertive partner, transfer blood from one person to another without becoming infected themselves.

However UK HCV specialist Sanjay Bhagani said he remained unconvinced, as a number of studies showed no association with fisting. He also thought that drug injection was becoming more popular amongst gay men and this may be spreading HCV.

a chance to dream

Emmeline Ravillious discovers what the Sussex Beacon and EJAF are doing about sleep disorders.

What have people with HIV consistently cited as one of the top three problems they have to deal with in life?

The answer is sleep deprivation. In both of Sigma Research's *What Do You Need?* surveys, sleep problems were the third-most frequent problem, experienced by a third of people in 2002 and 37% by 2008.^{1,2} In both surveys, the number-one problem has been sex, which is probably a coverall for issues ranging from impotence and body image to worries about disclosure and rejection. In 2002, the number-two problems were anxiety and depression, with self-confidence as number four; in 2008 these had swapped places.

But sleep kept its place, and this normally meant insomnia or waking up too early. Sleeping is not just a problem in the UK: an American survey found that no fewer than 73% of people with HIV qualified as poor sleepers.³

There are physical reasons for poor sleep in people with HIV. The surface shell of HIV acts as a nerve toxin in itself, producing disrupted and shallow sleep and increasing the amount of dreaming sleep.⁴ But HIV drugs can do this too, most notoriously efavirenz (*Sustiva*). Vivid dreams and nightmares are a well-known side-effect of this drug, especially in the first month or so after starting it, and the dizziness it produces in some people during the day may also be caused by sleep deprivation. It appears to cause sleep disturbance in the same way as HIV does itself, by increasing dreaming sleep and reducing refreshing deep sleep.⁵

Insomnia can be caused by other physical problems ranging from night sweats to muscle aches and itchy skin. But the biggest causes for insomnia are probably anxiety and depression, and this can become a vicious circle: anxiety and depression make you lie awake and worry,



David Furnish (right), pictured meeting Mick Sykes, Sussex Beacon's service user representative. Trustee of the Elton John AIDS Foundation (EJAF), David Furnish visited the Sussex Beacon and saw the work of the Sleep Service programme, funded by EJAF in October this year. EJAF has been involved with the Beacon since 1993 – originally helping to provide meals to people in the terminal stages of AIDS.

but the fatigue the following day can cause more anxiety and difficulty with performing tasks. As Sigma Research comments, "Worry generates insomnia, but insomnia also generates more opportunities to worry."

The Beacon programme

Given the severity of this problem, it is perhaps surprising it hasn't often been specifically tackled in HIV medicine before, especially as sleep medications can become addictive.

The Sleep Service programme provided by the Sussex Beacon, a clinical care centre for people with HIV, is an innovative programme for people who have been experiencing longer-term sleeping difficulties. The service aims to help people to regulate their sleeping patterns while, at the same time, reducing their dependence on sleeping tablets – often working with the prescribing doctor to manage this.

Advice from cognitive-behavioural counsellors, together with sleep diaries, allow users to establish a decent sleep regime remarkably quickly – often in just two or three weeks. This not only improves the physical health of the service user, but encourages a positive attitude for a happier, and healthier, future. One service user explains: "Tablets do not offer the same quality of sleep."

The scheme works hand-in-hand with an Anxiety Management Service, probing those anxieties that may contribute to sleep problems and helping people overcome fears. Nearly 100 people have been through the programme and all of them have been able to stop relying on sleeping tablets.

Common anxieties addressed in the programme relate to disclosure of HIV status, experience of prejudice and stigma, and settling into a treatment regimen, as well as fears – often ill-founded – that length and quality of life might be cut short. A reliance on sleeping pills, or alcohol and other drugs, can mean many individuals shut off emotionally and physically, at times not taking the anti-HIV drugs that could prolong their lives. Establishing and

maintaining a workable sleep pattern helps service users work on issues of self-esteem and to cope with issues as they arise – not just good for them, but for those around them too. As one client says: "It helps to give my partner a good night's sleep too."

Nacho, a Beacon client, explains he had become resistant to many of the antiretroviral drugs available and now needs to inject his current drug twice a day, a prospect that he found terrifying. He has managed to overcome his fears with the assistance of Jackie Titley, the head of the Anxiety Management Service.

Jackie explains: "[Counselling] is one of our major services. Whether people have been diagnosed for a long time or are newly diagnosed, all sorts of anxieties can arise – be it from concerns about becoming ill, about the drugs they are taking, or how to tell partners and families. Anxiety can become all-consuming and we help people to realise that they have the coping mechanisms to deal with the anxiety they are feeling."

Clients have also found the contact with other people with HIV invaluable: from discussions concerning new drug routines, to making friends and increasing their self-worth.

The Beacon has been providing services for people with HIV for over 15 years, either as inpatients in the ten-bed unit or through day-based health management services. They aim to help people make informed and positive choices about their own health care and treatment. The centre offers a 'step-in, step-off' care programme: no doctor's referral is needed. Service users welcomed the Beacon's open-minded and flexible approach, with the combination of inpatient and day services. Therapies including acupuncture, aromatherapy, massage and hypnosis are also on offer. Over the years, like many other services, the centre's focus has shifted from hospice care, to long-term care and services addressing quality of life. ■

Enduring vision

Very sadly Robert Key, one of the founders of the Elton John AIDS Foundation (EJAF) and, for fifteen years, its Executive Director, died in October following a long battle against myelofibrosis.

NAM owes particular gratitude to Robert and the Foundation. This newsletter was, after all, very generously funded by the Foundation over the last three years. It was EJAF's support that enabled us to relaunch HTU in 2005, improving its design and reshaping its content to address new and emerging issues facing people with HIV.

Robert was a wonderfully gentle yet passionate man and on meeting him you were immediately struck by his warmth, modesty and vision.

It was a vision that permeated the Foundation's work and one which EJAF is committed to continuing, particularly supporting cutting-edge and relevant services, and responding to the ever-changing needs of people living with HIV.

On these pages you can read about one such innovative service, a sleep clinic, recently opened at the Sussex Beacon.

EJAF is also supporting a major new project that Terrence Higgins Trust is embarking upon, in collaboration with NAM and George House Trust.

This will bring face-to-face treatment and health information services to five cities across the UK, closing the all-too-common gap that can appear between clinical and community or social services. We will bring you news of this exciting national project as it unfolds.

Caspar Thomson
Executive Director, NAM

can you help?

We are re-developing our website, **aidsmap.com** to make it easier for people to find information that is useful and relevant to them.

It is really important to us that we hear from those of you who use the website – and those of you who don't – to get your views and involvement in its development.

If you have access to the internet, could spare some time every now and then and would like to help shape aidsmap, please contact Zoë by emailing zoe@nam.org.uk or calling 020 7840 0053.



thanks to our funders

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Every year NAM provides information resources, like *HIV Treatment Update*, to thousands of people living with HIV, completely free of charge. To do this we really do rely on the generosity of people like you to help us continue our vital work. You can make a difference today. Please make a donation by visiting www.aidsmap.com/donate or by ringing us on 020 7840 0050.

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 Phonenumber**
An HIV treatment phonenumber, where you can discuss your issues with a treatment advocate.
0808 8006 013
Mon-Wed, 12pm-4pm