nam aidsmap

HIV treatment update

Issue 216
Final edition

HIV treatment update
Editor Gus Cairns
Sub-editing & proofreading Greta Hughson
Design Kieran McCann
Printing Cambrian Printers
ISSN 17567890

Charity number 1011220
***HIV treatment update* was founded by** Peter Scott

Contact details
77a Tradescant Road, London, SW8 1XJ
Tel 020 3242 0820
Fax 020 3242 0839
Email info@nam.org.uk
Web www.aidsmap.com

About NAM
NAM is a charity that exists to support the fight against HIV and AIDS with independent, accurate, up-to-date and accessible information for affected communities, and those working to support them.

For more information, and details of our other publications and services, please contact us, or visit our website, **www.aidsmap.com**.

In this issue

Gus Cairns
Editor

So here we are – this is the last issue of *HIV treatment update*. But it is not the end of the kind of features that *HTU* carried.

From now on you will be able to read interviews, news summaries and articles that analyse developments in HIV on our website, aidsmap.com. But it is the last issue of this printed newsletter landing on your doormat or waiting for you at your clinic.

We wish it wasn't so; but the drastic cuts to voluntary sector HIV funding that have been happening in the last two years, and which have affected NAM as they have other charities, mean we simply can't justify the cost of a printed newsletter any more – not if it's at the expense of our core mission to provide information and analysis in the most comprehensive way possible.

This happens at a time for HIV that is both immensely hopeful and fraught with danger. Globally, the most recent UNAIDS report reveals that, in overall terms, we may have turned the corner on HIV: both the number of people living with HIV and the number acquiring HIV every year are significantly declining, especially in the African countries with the great 'hyperepidemics'.

But at the same time, crucial groups of people are being left behind: HIV prevalence is still rising or failing to fall in many countries of the world, both rich and poor, in groups such as people who inject drugs, sex workers, transgender women and men who have sex with men. The danger is that, as HIV is increasingly confined to these populations, the stigma, discrimination and brutality that they face will be intensified.

Prominent voices in the HIV field, ranging from top researchers to Bono, have been talking about the "beginning of the end of AIDS" for the last year. Certainly there is much hope around, and in this final issue we've chosen to feature some of it, from progress towards a cure (page 12) to new discoveries in vaccines (page 16) to continued rises in life expectancy for people with HIV, now extending into poorer countries (opposite). But these will require continued extraordinary commitments, both to research and to strengthening health systems and maintaining the ones that work – including the UK's National Health Service, the subject of a challenging reorganisation that we also cover in this issue (page 4).

The biggest challenge in HIV now, though, has less to do with health and more to do with human rights. It always was, of course, but now we actually *have* the tools to end HIV it becomes much clearer that, if we are to do so, we simply *must* campaign to ensure equal access to the groups with the highest HIV prevalence. It's natural justice to do so but also it makes public health sense: otherwise we – and I write as a gay man – will be like the 'reservoir cells' in the body politic, always threatening to become the wellsprings of a resurgent epidemic.

Well, I write this from the AIDS Impact conference, one of the few that has always regarded social disadvantage, psychology and mental health as being key to ending HIV, because people who are excluded and terrorised can't access treatment and can't keep themselves safe. For the first time in years, this normally underfunded conference received significant support from pharmaceutical companies. Drug companies don't give money out of sympathy: they give it to initiatives they think will work, and they have realised that extending our knowledge of the social science of HIV is going to be crucial to ending the epidemic – and that includes finding out how best to involve communities in gathering and using that knowledge.

Knowledge is power. NAM's mission is to share knowledge, locally and globally. And as long as we can, we will continue to do so.

Upfront

How much longer have I got?

by *Gus Cairns*

We're concentrating on the future as a theme in this, the last-ever *HIV treatment update*. So it seems appropriate to have an update on exactly how much future we might have as individuals.

The last piece in *HTU* about life expectancy was written in 2010, in *How long have I got, doc?* (*HTU* 195). This reported that researchers in France and the Netherlands had found that some groups of people with HIV now had normal lifespans.

Since then, a number of studies have confirmed that life expectancy in people with HIV is continuing to catch up with that of the general population.

One study published only a few weeks ago[1] looked at increases in life expectancy in the US. In our 2010 article, we reported that life expectancy in the population with HIV was fully 21 years lower than in the general US population, due to racial and socioeconomic inequality.

This recent study finds that now, at the age of 30,[2] US men can expect to live another 47 years and women another 51 – in other words, expect to die on average at the ages of 77 and 81. (It always has to be stated what age the life expectancy is *from*, as you get a bonus simply by not having died.)

The same study found that in 1997, average life expectancy, even of those taking combination antiretroviral therapy, was only 21 years at age 26: so they could expect, on average, to die at age 47. By 2012 the life expectancy deficit had narrowed and people with HIV could, at age 35, have an expected lifespan of 63 years.

This is clearly still well short of the national average: but we are not comparing like with like. People with HIV are more likely to be male, more likely to be black (US black men die five years sooner than white men) and more likely to have higher rates of a number of life-shortening attributes ranging from smoking to suicide. If you compare like with like, the expected lifespan of HIV-negative people at age 35 in the US with the same demographic factors is only 72 years.

Still a nine-year age gap, though. What makes the biggest difference, however, is late testing. The surplus mortality seen in people with HIV is overwhelmingly concentrated into the first year after testing, when many may have a low CD4 count. The earlier people with HIV test, the higher our life expectancy will rise.

This US study found that expected lifespan in people with a current CD4 count under 200 was 66 but in people with a CD4 count above 500 it was 73, or one year above the comparator HIV-negative group.

> “What makes the biggest difference...is late testing. The surplus mortality seen in people with HIV is overwhelmingly concentrated into the first year after testing, when many may have a low CD4 count. The earlier people with HIV test, the higher our life expectancy will rise.”

Life expectancy for people with HIV in the UK is generally higher than this – and seems to be continuing to improve.

The average general-population expected lifespan at age 35 in the UK is 80.1 in men and 88.6 in women. In 2011, average life expectancy in the UK-CHIC cohort, a group of over half the people with HIV in the UK, was 75 if they had started ART at a CD4 count above 200 cells/mm^3.[3] But it was only 58 in people who started therapy with a CD4 count under 100 cells/mm^3 – such is the death toll due to AIDS in the first months after diagnosis that those 100 fewer CD4 cells take 17 years off life.

A UK-CHIC study, done a year later,[4] found that an HIV-positive man aged 35, with a CD4 count between 350 and 500, now had an average expected lifespan of 77 years; if his CD4 count was over 500, it rose to 81 years – statistically indistinguishable from the general population, and *not* adjusted for risk factors. There was even a hint, in another study,[5] that people with HIV who survive till age 60 may, in Europe at least, expect to have *longer* lifespans than the general population – though this evidence is as yet only based on a tiny group of the oldest people with HIV (wait until we're all 80-year-olds and we'll find out).

The most heartening life expectancy development in the last three years, however, comes from several studies that show that life expectancies in people with HIV are starting to become normal even in lower-income countries. A study from Uganda[6] found that the expected average lifespan of a 35-year-old with HIV was now 51 in men and 67.5 in women. This compares to a life expectancy at *birth* of 53 in men and 55 in women. Life expectancy at age 35 will be higher due to high child mortality rates, but still, these new projections are approaching equivalence to the general population. nam

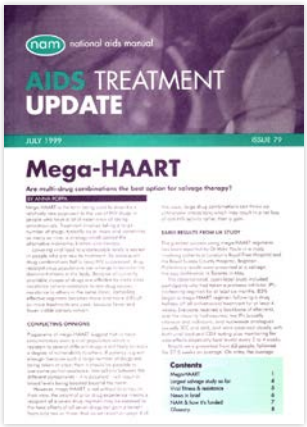
All cha

Where we've been and where we're going in

As part of the last-ever *HIV treatment update*, *Gus Cairns* asked a number of prominent activists, movers and shakers in the world of HIV care and prevention in England about how far we've come in the fight against HIV and about the challenges that remain.

ange...

HIV in the UK



The first edition of *AIDS Treatment Update*, as it was then, appeared in November 1992, during the worst years of the AIDS crisis in the UK. Yet 1992 also saw the first hints of hope. We still had several years to go before fully fledged combination therapy, but in *ATU* 1 there is an article about the relatively new idea of combining two drugs and mentioning the Delta trial, the first large scientific trial to show a significant reduction in mortality as a result of this combination – over 40% fewer people died of AIDS in a year if they took AZT (zidovudine, *Retrovir*) and ddI (didanosine, *Videx*), as I did for a while. The first issue also mentions nevirapine (*Viramune*), the first drug of a new class (non-nucleoside reverse transcriptase inhibitors, or NNRTIs), and a set of experimental compounds called TIBOL drugs – which eventually reached the clinic with the licensing of etravirine (*Intelence*), 15 years later.

HIV treatment now works so well that if people get tested in time and take treatment promptly, and if they manage to avoid other life-shortening habits such as smoking, they can live a normal lifespan (see *How much longer have I got?*, page 3).

Many people, of course, don't test in time and an HIV diagnosis – often combined with serious illness – remains a profound shock. People still die of AIDS and 40% of people in the world with AIDS even now don't get treatment.[1] But a lot of the problems we talk about now – especially in the resource-rich countries of the world, such as the United Kingdom – are the problems of success.

Are increasing rates of HIV in gay men driven by the perception that HIV is not life-threatening anymore? Will the quality of HIV treatment suffer if it is seen as a common infection that does not need specialists? Do people know less about HIV if it's less in the public eye? Is this paradoxically exacerbating stigma? Should prevention messages be more consistent and hard-hitting? How do we make HIV prevention more effective in an era of funding cuts? And how will we maintain a joined-together prevention and treatment strategy in a reshaped and part-privatised NHS?

I don't know the answer to any of these things, so I interviewed three people who might, or who have at least thought about the future of HIV services more than I have. They are:

- Dr Kevin Fenton, director of health and wellbeing at Public Health England.
- Professor Jane Anderson, former chair of the British HIV Association. She stepped down from this post in the summer of 2013 to become Public Health England's adviser on sexual health and HIV.
- Dr Richard Ma. A GP in Islington, north London, he is a longstanding member of the Royal College of GPs' Sex, Drugs and Blood-borne Viruses (BBV) Group.

I interviewed them separately, but since I asked the same questions I have edited their

replies together.

I also asked four other prominent people in the HIV sector in England – Lisa Power of the Terrence Higgins Trust, Professor Brian Gazzard of the St Stephen's AIDS Trust, Winnie Ssanyu-Sseruma of Christian Aid, and Paul Clift, a patient representative on the NHS England HIV Clinical Reference Group – about the story of HIV in the UK: how they feel things have changed over time and what they think the remaining key issues are.

What's the biggest challenge in HIV prevention in England now?

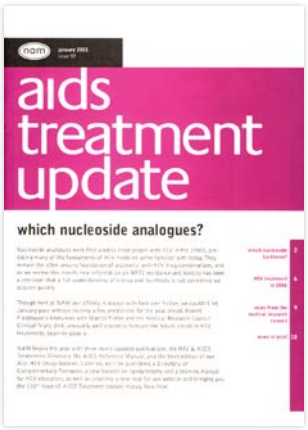
Kevin Fenton (KF): We need behaviour change, of two types. Firstly, we need a behaviour change in HIV prevention providers. There has been a revolution in our understanding of HIV prevention but we need to improve practice and get better outcomes in HIV testing, treatment and prevention. Service commissioners need to understand what high-quality services are actually composed of. Good, honest and impartial research and information is a critical starting point in this.

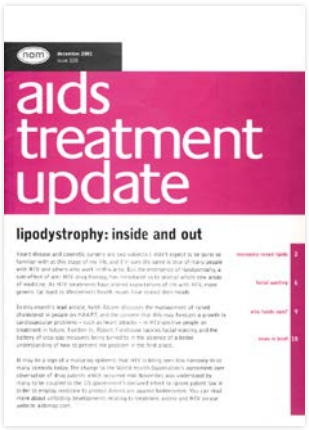
Secondly – how do we instil and maintain behaviour change in individuals? It's challenging but not impossible. Sixty per cent of gay men *do* consistently practise safe sex with casual partners: what can we learn from them? It comes down to the resilience we are able to build in men; to the sort of preparation we give to young gay men, so that they begin to become sexually active within a norm of safer behaviour rather than a para-norm of club drug culture, mental ill-health or other negative realities. We need to understand, invest in and support resilience.

Jane Anderson (JA): We have first-class treatment and care in England, but we need to understand how to extract the maximum prevention potential from it. How do the things that work, work best? The proportion of people with HIV who are on treatment and virally suppressed is now 58% and increasing, but the NHS is now entering a different health economy. This is a huge risk, and it will be a challenge to ensure there continues to be the same continuity of care from prevention campaigns through testing to treatment.

We've done a lot of research into how to ensure people don't transmit HIV. What we don't know enough about is how to prevent HIV *acquisition*. We don't know enough about how to help HIV-negative people stay HIV negative. We don't know what skills it takes; we don't know the trigger points for when people let down their guard and get infected. How we find that out and help people remain HIV negative is a very challenging area.

Richard Ma (RM): The biggest challenge is to hardwire into the consciousness of doctors and nurses that this is an infectious disease and that early diagnosis is key. Not everyone has symptoms when infected, but





HTU asked four prominent people in the HIV sector in England – Lisa Power of the Terrence Higgins Trust, Professor Brian Gazzard of the St Stephen's AIDS Trust, Winnie Ssanyu-Sseruma of Christian Aid, and Paul Clift, a patient representative on the NHS England HIV Clinical Reference Group – about the story of HIV in the UK: how they feel things have changed over time and what they think the remaining key issues are.

Lisa Power

When the original *AIDS treatment update* appeared in 1992, I was already very involved in HIV work and activism. Fundraising for HIV was unpopular; the Terrence Higgins Trust (THT – to whom I was then an external adviser on funding) was poorer than the Poor Sisters of Clare. The Red Ribbon had recently been invented as a symbol; already people were arguing over who owned it.

A bunch of gay men resigned from the government's Health Education Authority because it wasn't doing enough for gay men, who were over two-thirds of all people who'd been diagnosed so far. THT had independently begun producing new booklets, using real models from the gay scene, which were far more popular and accurate than the government materials, but their stance wasn't urgent or radical enough for others, who in turn left them to found GMFA [the organisation previously known as Gay Men Fighting AIDS] that year with much more explicit material. There was hot debate over what you could get away with printing; the "angle of dangle", or how erect a penis was, was a key factor in whether the police might seize materials. GMFA, if they don't mind me saying so, had the biggest and straightest dicks in town; I never looked at my flatmate (their first model) in quite the same way again.

Family & Youth Concern had produced a schools video that claimed heterosexual

in one study in which they systematically HIV-tested people who had suspected glandular fever, they found quite a high proportion of it was in fact HIV. However, it's not just about compiling a list of indicator diseases; it's about making testing for HIV a normal thing to do. One way might simply be to include an HIV test as one of the boxes you have to tick on hospital admission forms; we could do a trial to see if this actually made healthcare workers more likely to test people.

HIV treatment is now nationally commissioned, but sexual health and HIV prevention are now not even within the NHS but the responsibility of local government. How do we integrate HIV treatment and prevention from now on?

KF: We're going to have to work across organisational boundaries. The sexual health framework from the Department of Health[2] certainly sets out useful ambitions

> "The new NHS will be outcome-focused and that means you don't concentrate on things like the number of HIV tests you administer – the outputs – but on real clinical outcomes."
>
> **Professor Jane Anderson**

to guide us, but HIV demands more from us because of its complexity. Yes, we have a new prevention campaign for England, but how does this link with getting the person through the doors to test, and then through another set of doors to be treated if they test positive? Perhaps most critically for the future, how can we integrate medicine-based prevention, like PrEP [pre-exposure prophylaxis], into this? Although we are still by no means sure of PrEP's effectiveness, I think we have an obligation to see if it works because so little else does for gay men.

JA: The fact that most HIV testing is now in the grasp of local authorities has some advantages. Taking sexual and reproductive health out of the NHS wasn't an accident. We now have some geographically based power, at least in areas where enough local politicians are sympathetic towards prioritising sexual health, as they are in my local borough of Hackney. So there is an

transmission was virtually impossible, but oral sex and condoms were dangerous. The Health Secretary had received a report that some health authorities were diverting money for HIV into other areas, and many of them were ignoring local epidemiology to spend it on those less at risk but more politically acceptable. Journalists were hounding Holly Johnson, who they'd heard might have AIDS, but virtually nobody famous was open about their diagnosis and still alive, bar Derek Jarman.

Yet in 1992 we were also on the verge of finding antiretroviral treatment that worked; HIV money was wasted, but there was plenty of it to go round if we could only get a grip on it; groups that squabbled could easily go off and found something else in the knowledge that there were enough volunteers, community spirit and enthusiasm for all.

In 2013, partly because of antiretroviral therapy, we have ten times as many people with HIV but we don't have ten times the money – or ten times the community involvement.

HIV has become too familiar to some and forgotten by others. We might have hated the government campaigns, but at least something kept the whole country reminded about HIV. There are many things that are better in 2013: people with HIV can live to old age; generics are round the corner and should cut treatment costs considerably; we have far better legal protection for people with HIV in the UK; and the internet has brought peer support a very long way.

But there are far fewer resources and ignorance still cuts deep.

So, in another 20 years' time, will we be saying farewell to our best-loved HIV websites, as we are now to the well-loved *HTU*, because something else has come along technologically? Will HIV be so normalised that, like cancer before us, we've massively reduced stigma? Will we be using our smartphones to diagnose STIs? Will treatment be a six-monthly implant? Or will inequalities be even greater and the money even more thinly spread?

Whatever the future holds, it's in all our hands. And if I'm still alive then, which is debatable, I'll probably still be using the same slogan I clung to in 1992 as my friends died, and I use in 2013 as I try not to cling on to historical mistakes – "Don't mourn, organise". History is fine, but only if we learn from it. And, preferably, interfere with it.

Lisa Power MBE is policy director of the Terrence Higgins Trust.

opportunity there to ensure that services commissioned, including prevention messages, will more closely fit local needs.

Local clinicians have a role here. They can advise local politicians: "Here are the outcomes you need to hit: these are the indicators of whether you are addressing local sexual health needs or not."

But the huge pressure on local authority budgets may mean that they won't focus on HIV or, worse, that bringing sexual health into the control of local politicians will politicise it. While they are required to commission local sexual health clinics, they're under no obligation to mount HIV awareness or testing campaigns. It's less controversial to encourage wearing seatbelts instead.

There are some sticks built into the system. The local director of public health is there to guide local authorities and they need to adhere to the Public Health Outcomes Framework (PHOF). The new NHS will be outcome-focused and that means you don't concentrate on things like the number of HIV tests you administer – the outputs – but on real clinical outcomes like changes in the average CD4 count in those diagnosed.

I don't know how much clout the PHOF will have if local authorities miss their targets, though the Secretary of State retains a power to ensure that public health is equitably addressed. Outcomes are also harder to measure than outputs; there is inevitably a time delay between implementation and outcome. If a local authority is missing its target, will we notice it too late?

> "We have too many undiagnosed people in England and need to get creative in how we offer testing: move outside the clinic and look at community-based testing and home-based testing and sampling."
>
> **Dr Kevin Fenton**

RM: Sexual health is back where it was before the NHS, when it was the local VD [venereal disease] service run by the local borough. Politicisation is a real threat, and not just to HIV: local authorities will also be responsible for providing abortions and teenage contraception. However, I do think the PHOF, and even politicisation, can be

Professor Brian Gazzard

It must be very unusual for a doctor to see a brand-new disease developing which is almost uniformly fatal and during his working career to see the same disease become a manageable condition with a good chance of people with it living a normal lifespan.

I have given much thought as to why this miracle happened. Firstly, we were very lucky. Had the AIDS epidemic started 20 years earlier, which it might well have done, we would have had little knowledge of retroviruses, of the function of lymphocytes, or had much of a technology to allow such rapid advances in treatment and care.

Secondly, it is a tribute to a National Health Service (NHS) which, despite our impoverished state, remains the envy of much of the developed world. We must ensure that the organisational changes in the NHS do not destroy this.

I am hopeful. During my 30 years as an NHS consultant, we have survived numerous re-organisations and will do so again. I would also like to pay tribute to the voluntary sector and to constructive activism, particularly in the UK and the USA, which has involved some of the brightest minds in pushing new treatments, for care and for a relatively non-prejudicial framework in which treatment and care could be provided.

The revolution in HIV care has been a wonderful example of basic science and the pharmaceutical industry collaborating to produce drugs that attack the virus, though recognition that lifelong treatment needed to be both convenient and tolerable may have been somewhat belated. While not perfect, present treatment does offer relative freedom from serious side-effects for the vast majority.

Many challenges remain. I think there are some glimmers of hope that a preventative vaccine might become available. Personally I think this is a more realistic prospect than a cure for HIV infection, though people would obviously like to be cured of their infection rather than merely controlling it. A cure is an unbelievably difficult and long-term goal – but then I would have said the same thing about treatment in 1983.

When you look at patients on the ward now, the primary problems are patients who come without realising they were HIV positive until a late stage, and a few

useful: it is amazing how much pride, not to mention economic advantage, a local authority can derive from having a low teenage pregnancy rate!

How will national commissioning of HIV treatment work?

JA: We'll have a national service specification for HIV for the first time, informed by existing service standards such as the BHIVA and MEDFASH ones. The NHS National Commissioning Board (NCB) will delegate commissioning to Programmes of Care (PoCs) that will actually commission specialised services. The PoC that includes HIV, however, also includes cancer and blood disorders; you can bet that if there is any spare money around due to savings when generic [HIV] drugs come in, it may not get ploughed back into HIV services, but into cancer drugs.

Advising the PoCs, though, you have Clinical Reference Groups (CRGs) for each condition. These are potentially powerful bodies; they include patient reps and the chair of the HIV CRG is Simon Barton, clinical director of the largest HIV and sexual health clinic in the UK. Regional reps in the CRG are themselves supported by local groups of physicians – so-called Clinical Senates – who are there to advise them on local issues. There is also a specific national commissioner for HIV, Clare Foreman, who used to head the London Specialised Commissioning Group. Altogether, I think it's a pretty coherent structure, or should be.

RM: I think one of the problems about the new structure is that the people who will be doing HIV testing won't witness the clinical benefits of it. Those of us who know about the issues will have to do a lot of gathering, framing and communicating evidence and we have ways to feed into the local agenda. It will be about jostling for attention. I have become an ardent tweeter, following people who matter and making sure they get fed information and evidence about the benefits of good testing and treatment for HIV.

What's the best way of getting more of the right people to test for HIV, and to do it regularly?

RM: Between 2004 and 2012 sexual health could be included in the Quality and Outcomes Framework (QOF) for GPs; sexual health outcomes started to become part of the incentive structure for some GPs. This is no small thing: QOF incentives make up a third of GPs' income. The scheme expanded from contraception and conception advice to 'enhanced services' such as, for instance, a substance misuse service, allowing them to prescribe methadone. They could also bid to run an expanded sexual health service. This was defined nationally in rather vague terms, but in my local area, Islington, a scheme was set up whereby GPs were incentivised to test for HIV and were paid

individuals who cannot tolerate any of the medications available. We need to be much more proactive in involving the social scientists in determining how best to test for HIV at appropriate times and in environments which the patients find acceptable, and also to understand more clearly why some people just cannot tolerate taking medication.

Finally, of course, we should not forget that, despite rapid advances, nearly half the HIV-positive population in the world are denied treatment and some still get drugs with side-effects no longer seen in richer countries. Continuing medical, activist and political advocacy will be needed to continue to make inroads into this epidemic.

Professor Brian Gazzard CBE is chair of the Department of Health's Expert Advisory Group on AIDS and research director of the St Stephen's AIDS Trust.

Winnie Ssanyu-Sseruma

The advances in HIV treatment have fundamentally changed the lives of many people living with HIV and, to a great extent, the global health landscape. In the 1980s, anyone who was known to have HIV not only had a short life expectancy, but many experienced stigma and died horrific deaths.

When I was diagnosed with HIV in 1988, I felt like death wasn't far off; I was filled with fear, really not living but just going through the motions.

In the 1990s, when combination therapy arrived, there was much-needed hope. Although physically my treatment worked liked a charm, what I didn't count on was how difficult it was psychologically to shift my mind from wondering when HIV was going to kill me, to living longer with it. Through therapy and other social support I was able to live again.

Twenty-five years on from my initial HIV diagnosis, the last decade has been about supporting others to access the services they need, speaking up and moving from working on HIV at a national level to an international one. I have learnt a lot through HIV activism (not all the learning has been about HIV), enabling me not only to get my life back, but to thrive.

Despite lingering challenges of HIV-related stigma and late diagnosis, I have seen a transformation in attitudes within the African communities in the UK. Some

for diagnoses of STIs [sexually transmitted infections], including HIV.

Unfortunately, this particular pilot ended with the new structure, which I think is a shame. The new structure does have illogicalities built in: for instance, the local Clinical Commissioning Groups run abortion services, while the local authorities provide the contraceptives that prevent women having to get abortions.

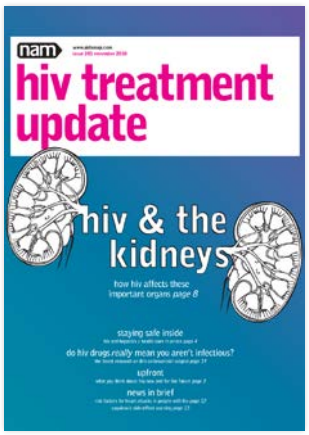
But in this practice, we still test patients regularly for HIV and have had two diagnoses in the last month. We have diagnosed gay men here but we usually see black Africans as they are less likely to use STI clinics and are more likely to get diagnosed late. The new PHOF [Public Health Outcomes Framework] tells local authorities that reducing late HIV diagnoses is a good thing, but won't push proactive testing in primary care as it's not cost-effective. This is a pity: GPs might be good at working with the "won't-testers" as they may see patients regularly and are very good at exploring health benefits and challenging beliefs.

KF: We have too many undiagnosed people in England and need to get creative in how we offer testing: move outside the clinic and look at community-based testing and home-based testing and sampling. We also need to plan for scale and to manage for scale: we can't tackle the problem of the undiagnosed by viewing it as a matter of an initiative here, an initiative there. The other thing I'm really committed to doing is to ensure Public Health England begins to pull people together to have a bolder ambition for better HIV and sexual health, especially gay men.

Is there a reason why primary care physicians (GPs) seem to be reluctant to deal with HIV?

JA: I don't think we really yet know why healthcare workers are reluctant to test people for HIV. I think it's something to do with the disease's psychological and cultural meaning: doctors should be used to giving people bad news, but in this case they feel they lack the skills, which I think is actually a myth. They think they'll have to be sexuality counsellors or start exploring risk behaviour, but the doctor is the last person who should do that. It's not their job to ask their patient how they got HIV, it's their job to inform them they have a medical condition and treat it appropriately. I find once doctors give an HIV test result a few times, they feel skilled again – it becomes incorporated into 'the things doctors do'.

RM: I think it's historical. HIV started off as a very specialised and marginalised area that was the province of a few dedicated specialists; some other doctors still see it in that light. The important thing is not to force doctors to work out of their competence but to ensure you have integrated care. In other areas, diabetes, asthma, arthritis, even



faith leaders have become HIV activists, something seen as close to impossible in many people's books. Because African and gay communities have been most affected with HIV, it made common sense to work together. I really feel that this partnership has helped to put a dent in homophobia in African communities, although I admit there is still a long way to go.

There are still a few worrying issues. HIV information campaigns and testing levels are nowhere near where they should be. We know that those living with HIV who are not aware [of their status] or not on treatment are more likely to pass on HIV than those on treatment. And there are millions around the world who need treatment now and are unable to access it. But funding levels for anything HIV-specific have declined and HIV support organisations are either cutting back or closing down altogether. The stigma attached to living with HIV is still rife, especially in rural areas – not just in the UK but in various parts of the world.

I am concerned that if there isn't the same level of investment in HIV globally there might be another HIV epidemic on the horizon. Many funders have now moved on, way too quickly, to funding other health issues. HIV remains an unfinished agenda and, if not dealt with properly, may unleash a second wave of HIV that may be more lethal than what we have been dealing with for the last three decades.

Winnie Ssanyu-Sseruma is senior policy and advocacy officer for community health within the Africa Division at Christian Aid. Back in 1996, she was the first African openly living with HIV in the UK to appear on the cover of a national magazine.

Paul Clift

I was diagnosed with HIV in 1988 and became increasingly involved in the field of activism from the early 1990s following the death of my partner.

What has changed since then? Almost everything, it seems. The main change is in treatments: when I was diagnosed there were no treatments, now there are many. Not only that, the meds we now have are comparatively tolerable and easy to take. That is a very big change, hugely

areas with more social meaning attached like schizophrenia and drink and drug misuse, GPs are quite happy to do the day-to-day management. There's no reason they couldn't do this with HIV as long as they had specialists to deal with HIV therapeutics and monitoring.

How do we check on quality in the new NHS and other health services? Especially privately run ones?

JA: Everything will depend on the right contracts with the right service specifications. There is nothing wrong as such with, say, Sainsbury's running your hospital pharmacy, as long as the commissioners have been specific about what they want in advance, HIV specialist pharmacists are included in the tender, and patient reps are consulted and are clear about what *they* want. It all depends on what people are contracted to do: the same people may be doing the same job but may be subcontracted and managed administratively by a private firm. You need proper clinical governance and auditing, hence the importance of a national service specification for HIV. If you are in a structure where there are a lot of competing providers, they have to deliver the right stuff or they won't get more contracts. A lot of third-sector providers may actually be more used to operating that way.

How do we preserve what is acknowledged to be an excellent HIV treatment service?

JA: I know of few other treatment areas that have issued such detailed standards describing what good care looks like. Clinical standards are not just there for the benefit of doctors but also for patients, as a collaborative tool. I do worry about patients getting a worse service if we unpick HIV integrated care, but if doctors and patients can work together collaboratively and point out that standards now enshrined in the NHS are not being met, then that is at least a tool for trying to ensure that won't happen.

KF: In prevention, I think we just have to be really clear from the start about what objectives our intervention, whether it's a testing pilot or an information campaign, is trying to achieve. Then we learn about whether that resource is meeting its intended objectives as we conduct it. I don't think in England we've done a very good job about evaluation, about continuing to learn as we implement. We have a good toolkit of HIV interventions but there is not enough evaluation and we have to build our knowledge of what we know works. We should also keep our eyes open for new interventions – PrEP, home testing for example – that can help us approach very complex and 'wicked' problems in new ways, and commit to evaluating those innovative solutions too.

significant, because it means that a well-chosen first regimen can last for many years. I've not altered the regimen I started with seven years ago; it still does the trick with no noticeable side-effects.

That means that a person with HIV now has a good chance of living a good life. That is easily the biggest change. It's now possible to do more than merely exist, more than clock up years of 'long-term survival'; it's possible to get out there and achieve things in life.

In terms of current challenges, the privatisation of the NHS is a potential one. The pharmacy at King's has gone over to Sainsbury's and the specialist HIV knowledge would have gone if we had not been able to keep it in the HIV outpatient clinic; still many, though not all, patients will have to traipse over to the new generic pharmacy to collect their meds.

As for national commissioning, the government was persuaded to let HIV remain 'specialist' and therefore a national rather than local priority, for clinical reasons – but that 'national and specialist' designation can change at any time. Also, the Clinical Reference Groups are thinly funded even now and one has to be pretty robust and insistent to get a community voice heard at all in an online virtual meeting.

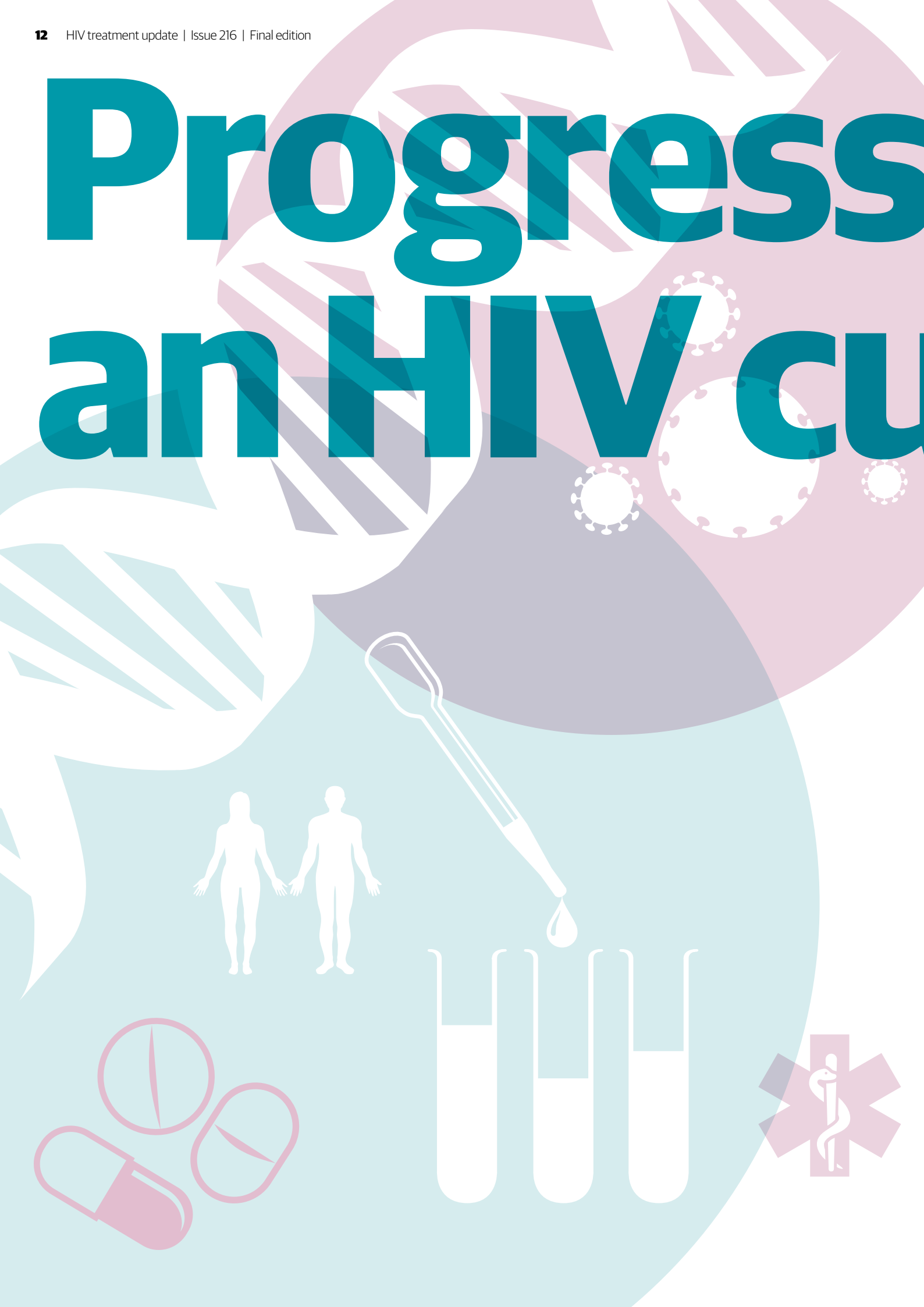
The biggest change is still in the future, and it's a change that we're not prepared for. Thanks to the success of treating Timothy Ray Brown, the man cured of HIV, it is now possible to consider cure as a possibility.

The assumption is that such advances are 'simply' good when in fact they are 'complicatedly' good. The introduction of ART saw genuine advances in people's health, but was accompanied by a significant level of mental health problems in people who by then had become massively bereaved by AIDS; the profound depression, with survivor guilt, close to being an acute post-traumatic stress response. None of us saw it coming. It hit some people hard, and continues to do so.

My fear is that when a cure does finally arrive, there will be a rush of people genuinely ready to take it (that's the 'simply' good) but others may or will experience a resurgence of the bereavement-laden depression exacerbated by a failure to come to terms with their position (the 'complicated' good). And that raises my deeper question here: how much do we, as activists, really take good care of each other? It seems to me that the arrival of the cure will be less a time for 'strong' activism and more a time for 'kinder, gentler' activism that celebrates and reflects and also allows time for recovery.

Paul Clift is patient representative at King's College Hospital in south London, and one of the patient representatives on the national HIV Clinical Reference Group.

Progress an HIV cu



towards ire

Gus Cairns scans the horizon for an HIV cure.

The last time I wrote a review of the progress researchers are making towards a cure for HIV (see *Towards a cure for all*, *HTU* 203 and *HTU* 204), it was 2011, in the wake of the first documented cure of someone with HIV.

Timothy Ray Brown, also known as the 'Berlin patient', had apparently had every trace of active HIV infection removed from his body by means of a bone-marrow transplant containing T-cells resistant to HIV infection. Brown's case showed that we *could* cure HIV: but clearly we will need safer, simpler and cheaper ways of achieving the same goal (the transplant, which Brown needed anyway for leukaemia, nearly killed him).

Different patients, different cures

Since then, there has been exciting progress in some areas – including announcements of a few more cases using the same and other strategies. However, it is becoming apparent that there may be no one single cure mechanism for HIV.

We may start achieving cures earlier in two groups of patients. Firstly, for people like Brown, whose condition ethically allows the sort of 'nothing to lose' procedure he underwent. Secondly, in people whose HIV is diagnosed very soon after they are infected, where there are signs that using antiretroviral therapy (ART) from the start may suppress HIV reproduction so fast and so deeply that it never really gets going.

Some of these 'cures' might better be termed 'remissions', because we do not know whether HIV will reappear at some point in the future: there may remain a tiny number of infected cells in the 'reservoir' of long-lived, quiescent T-cells, and it is possible they could be reactivated in the future.

The rest of us, though – those with chronic infection, who may be living healthy lives on ART but who would rather not have to take it – may have to wait considerably longer before a cure comes along.

More transplant cures – but one important failure

In a few people with cancers, similar cures to Brown's have been achieved. At a 2013 pre-International AIDS Society (IAS) conference symposium, *Towards an HIV cure*, researcher Dr Timothy Henrich told delegates that two people with HIV in Boston, who received stem-cell transplants for the treatment of lymphoma, had been maintaining undetectable HIV viral loads without medication for 15 and 7 weeks respectively.[1] The decision to take them off ART was only made after the most sensitive available tests failed to detect any HIV genetic material in their cells.

The approach taken here was relatively less toxic than that used for Brown. He had his entire immune system effectively deleted with strong chemo- and radiotherapy before receiving a bone-marrow transplant of new immune cells with the so-called delta-32 CCR5 mutation, which occurs in about 2% of northern Europeans and means they are almost completely resistant to HIV infection.

The Boston patients received an immune-suppressant regimen that consisted only of chemotherapy, and the stem cells were from genetically matched donors without the delta-32 CCR5 mutation.

How did this produce a situation where no more than one in 200,000 immune-system cells in the blood were the patients' original cells and there was no more than one copy of HIV DNA in 15 million cells?

When we receive a transplant – whether of stem cells or of an organ like a liver – our body recognises it as 'foreign' and, unless the parts of the immune system that destroy foreign tissue are suppressed, the transplant can fail. Sometimes, however, the graft's cells start waging war on the native tissue in what is called graft-versus-host disease (GVHD).

That's what the researchers believe happened in these cases. "For six to nine months after the transplant, we see a mingling of the donor and host cells, and what happens over time is that the donor cells clear out the host cells." It had been important to keep the patients on ART during this time, Henrich added, as it protected the donor cells from infection with HIV.

However, he warns: "This is not a practical strategy that we can do for most people with HIV. Stem-cell transplantation is dangerous. There can be up to 20% mortality associated with stem cell transfer in the first year after transplantation".

This danger was underlined earlier this year. Doctors in Minnesota used a similar strategy to the one that cured Brown in a twelve-year-old boy with HIV and

leukaemia. They used not bone-marrow cells but stem cells – immune system progenitor cells – found in the blood from the umbilical cords of newborn babies, containing a rich supply of foetal stem cells that can be nudged into turning into a wide variety of cell types. The researchers found enough cord blood with the delta-32 mutation to give these to the boy.

Unfortunately the boy, Eric Blue, lived for less than three months after his transplant.[2] The GVHD that in the Boston patients had wiped out most of the remaining HIV-infected cells had, as it can sometimes do in transplant patients, turned lethal: the donor cells mounted a devastating attack on Eric's body.

'Functional cures' after early treatment

In people with chronic HIV, then, we have only achieved cures in a few people where high-risk, complex measures are ethically possible. This year, however, a number of cases of apparent cure or long-term remission from HIV turned up in people subject to a more benign technique – antiretroviral therapy.

In the first report, the talk of the Conference on Retroviruses and Opportunistic Infections (CROI) in Atlanta in March 2013, US researchers identified a case of a functional cure in a baby girl infected with HIV (the 'Mississippi baby'), who began ART within two days of birth.[3] The child has now been off treatment for 18 months, and although HIV DNA (genetic material) has been detected at very low levels in her cells, she has no detectable viral RNA in her blood and her virus is not reproducing – the definition of a functional cure.

The apparent suppression of the girl's HIV to levels below which it could start replicating – either because there was no fully functional HIV DNA left, or because her own immune system was controlling any remnants – was initially greeted with some scepticism. Was the HIV truly an infection, or residual maternal virus? Would HIV eventually reappear? There was nervousness about the claim of researcher Deborah Persaud that "This is our Timothy Brown moment". Even if this was not an isolated case and could be repeated, few people get the chance to start ART within days of infection.

However, a study published soon after CROI confirmed not only that long-term off-treatment remission of HIV was possible, it might even be quite common – and that ART did not necessarily have to be started within the first day or two. French researchers[4] found 14 (now 26) adult patients from a group called the VISCONTI cohort who also started ART soon after infection,

> "In normal HIV infection, even in people on ART, residual HIV – burning away like a pilot light – remains; as soon as ART is removed it 'lights the fire' again, stimulating cells into producing a new burst of HIV."

subsequently stopped it, and had not had to re-start because they had largely – and in eight cases completely – maintained undetectable viral loads for four to ten years after stopping therapy.

Furthermore, the researchers suggested that the only reason such cases are not more common is simply because, once having started ART, few people stop. They claimed that 15% (later revised downwards to 5 to 10%) of people with HIV, if ART was started within six months of HIV infection and maintained for at least a year, could subsequently become so-called 'post-treatment controllers'.

Their estimate is a stark contrast to findings from studies conducted between 1996 and 2000, soon after the introduction of highly active ART, which found no evidence that people who began treatment in primary infection soon after acquiring HIV could control HIV after stopping treatment. The key difference is that earlier studies looked at HIV control in people who had only received treatment for 12 to 18 months. The French patients had been on treatment for an average of three years before stopping, and all started treatment within ten weeks of infection, compared to within six months in previous studies.

A further study, presented at the IAS conference, came up with another patient – a 67-year-old German man – who had started ART within three months of infection and stayed on it for five years, but who stopped his HIV therapy in 2004 and, apart from a small initial viral 'rebound', has not had a detectable viral load result since.[5]

This patient's CD4 and CD8 cells had strong anti-HIV responses, meaning his immune system was actively preventing viral replication. This is also characteristic of 'elite controllers', people who maintain undetectable viral loads without therapy and, essentially, generate their own long-term remission from active HIV.

Being an elite controller might not be good for you. Another presentation at the IAS cure symposium found that HIV responses in elite controllers were characterised by increased activation of virus-fighting proteins such as interferon alpha which, as anyone who has taken it as hepatitis C treatment knows, creates symptoms of its own.[6] Another found high levels of a second immunomodulator with known harmful effects called galectin 9.[7] Elite controllers don't just experience physical malaise: it had already been shown that they have higher levels of cardiovascular disease than average, similar to other people with HIV not on ART.[8]

The VISCONTI researchers found that the viral control seen in their patients (and the Mississippi baby) had almost an opposite explanation from that seen in the majority of elite controllers, whose immune cells tended to be rather unresponsive to HIV. Infection spread slowly through the body, which allowed the immune system time to recognise HIV and mount a vigilant response to it.

In contrast, the VISCONTI patients' immune cells were unusually *sensitive* to HIV infection and their acute HIV infection period was characterised by high viral load. HIV invaded so fast, it gave their immune systems no time to react. Normally, this would result in the body being 'seeded' with a large reservoir of HIV-infected CD4 cells that would start pumping out virus as soon as viral suppression with ART was removed.

The theory goes that, if ART is started quickly enough and maintained for long enough, the viral reservoir remains small. In normal HIV infection, even in people on ART, residual HIV – burning away like a pilot light – remains; as soon as ART is removed it 'lights the fire' again, stimulating cells into producing a new burst of HIV.

In the VISCONTI patients, on the other hand, there was so little HIV around that, when ART was taken away, the immune system – which, remember, had never been given time to 'recognise' HIV – simply acted as if it was not there at all.

At the IAS cure symposium, Persaud mentioned unpublished data showing that a number of the other children she has studied might be in the same position as the Mississippi baby – but after a decade on ART, rather than 18 months. In some cases,

HIV DNA that was still detectable when the children were six or seven years old could no longer be found at twice that age.

This presents an ethical dilemma. The Mississippi baby case was only identified because the girl's mother stopped coming for appointments when her daughter was 18 months old, reappearing six months later. Similarly, the VISCONTI patients had taken themselves off ART voluntarily, often in structured treatment-interruption studies. Other people who have come off therapy in the past, however, have experienced disastrous crashes in their CD4 counts; at the very least, a viral 'rebound' upon stopping treatment will replenish the reservoir of persistently infected cells.

So how do we decide who to take off therapy? What is the threshold for judging that a person is a potential viral controller? Are HIV DNA counts the best guide? Or is the disappearance of HIV antibodies, as happened for Timothy Brown and the Mississippi baby but not for all the VISCONTI patients, a better guide?

Strategies for chronic HIV infection: kick, kill, contain

Most people who start ART later, however, are unlikely to achieve control of their HIV without more help because their reservoir of persistently infected cells is bigger, having had longer to be 'seeded'. Several approaches are being tried to halt ongoing infection, but the one that has received the most attention has been the so-called 'kick and kill' approach.

Initially, gene-stimulating drugs would be taken that 'kick' the normally quiescent central memory reservoir cells into becoming activated and producing some HIV. As long as this remains suppressed at controllable levels with ART, the hope is that by becoming activated, the cells turn into 'effector' cells with short lives; they die, and the reservoir is drained.

It would need to be drained very well: one study where HIV reappeared in someone with fewer than two-in-a-billion HIV-infected reservoir cells[9] shows that spontaneous control is unlikely to be perfect in all cases and that there may need to be further stages where drugs are taken that seek out and kill off the activated reservoir cells, driving their number down still further. Then something like a therapeutic vaccine might be given that magnifies the body's natural immune response to HIV and contains the activation of the tiny number of remaining HIV-infected cells.

The class of drugs furthest along in investigations into reservoir-cell activators are called HDAC inhibitors. Some are already in use as anti-cancer drugs. Professor Martin Tolstrup of Aarhus University in Denmark summarised his team's recent research at the IAS cure symposium.[10]

This research was the subject of an article in the UK's *Sunday Telegraph* which implied in a misleading headline that a cure for HIV might be achieved "within months". The team issued a correction and the article was subsequently modified – but it is evidence of huge public interest that these 'hope for a cure' articles keep appearing.

The researchers gave 15 men with HIV twelve doses of an HDAC inhibitor called panobinostat over eight weeks. They found that, after the first dose, 60% of participants expressed low but detectable levels of HIV RNA in their blood, despite being on ART, compared with only 28% before panobinostat.

The team will publish data on HIV RNA and DNA detected within cells soon, and will test groups of reservoir cells to find out how many remain with hidden HIV infections and how many can produce replication-competent HIV. The hope is that, if the panobinostat can drain the reservoir sufficiently, it might be safe to take people off ART for a monitored treatment interruption.

As mentioned above, we may need additional therapies that actively seek out and destroy the cells activated by immune stimulants such as HDAC inhibitors.

Dr Victor Garcia of the University of North Carolina introduced such a cell-killing missile at the IAS conference.[11] In this molecule, a broadly neutralising antibody (3B3) that attaches itself exclusively to HIV surface proteins, is joined on to a toxin, (PE38, derived from the *Pseudomonas* bacterium). The antibody attaches the molecule to activated cells from which HIV is budding and the toxin enters the cells and kills them.

This molecule was injected into mice that had been infected with human HIV. Three weeks later they were started on ART. Four and five weeks after that they were given two doses of 3B3-PE38.

Even though ART dramatically suppresses production of HIV within immune cells, some still remains. The ART, as expected, produced a hundred-fold drop in HIV RNA inside cells, but the bacterial toxin produced a further 6.5-fold drop (0.8 logs) on top. More importantly, the absolute number of cells expressing HIV RNA decreased from between 1100 and 20,000 per gram of tissue to between 600 and 3000 per gram, an approximately six-fold drop in the presumed size of the reservoir.

Genetic cell manipulation, immune therapies and therapeutic vaccines that contain any onward infection of HIV from activated cells to other cells may also be a crucial part of the 'kick and kill' strategy, both to encourage the body to kill or contain the tiny fraction of HIV-infected cells left after reservoir 'draining' and to prevent onward infection of HIV into new cells during the 'kick' phase.

These therapies are potentially safer than the hazardous cell-transplant approach, because many are based on what is called autologous transplant. Cells are taken out of the patient's own body and then genetically modified in some way – to make them immune to HIV or to stimulate an immune response to HIV – and are re-injected. This introduces a new population of cells into the body but not one that risks rejection or graft-versus-host disease.

In *HTU* 206, writer Matt Sharp recounted his experience of receiving a transplant of his own cells that had been genetically modified to be immune to HIV: the 'graft' became a large proportion of the immune system in most participants in the study and, in Matt's case, it also improved a persistently low CD4 count.

Autologous transplants can also be used as a form of therapeutic vaccine. In one study presented at the IAS conference by the Institut Pasteur in France, the immune-system cells called natural killer (NK) cells, which represent the body's first line of defence against viruses, were used.[12] When these sensitised NK cells were mixed with CD4 cells, 'virgin' dendritic (immune system) cells and live HIV, their presence reduced the proportion of dendritic cells infected with HIV from 45 to 25% and of infected CD4 cells from 35 to 20%. These reductions might not sound big but they may be enough to contain residual viral replication in a person whose reservoir of hidden HIV-infected cells has been depleted by the previous methods.

More impressive was the performance of a vaccine which used HIV components wrapped inside a cytomegalovirus (CMV) shell. When given to monkeys before infection with the simian form of HIV, this vaccine produced a stunted infection which eventually dwindled to nothing (see *The monkeys' tale*, page 16).[13] The researchers speculate that if this vaccine is safe and effective in humans – and that's a big if – it might form part of a cure too.

These experiments are in very early clinical or pre-clinical stages, and are just a sample of a whole number of experimental approaches designed to drive ongoing HIV infection down to the absolute minimum. In the long run, they may make it possible even for people with chronic infection to come off ART for long periods – and maybe even a lifetime – without HIV reappearing. Then we really would have a cure. nam

The monkeys' tale

How a vaccine might nip HIV in the bud

Four dozen rhesus monkeys may have successfully fought off the monkey equivalent of HIV in a series of trials of what looks like the most powerful candidate vaccine for HIV to date.

But exactly as many of the monkeys did not respond to the vaccine, and the researchers are pondering how to turn a vaccine that's powerful for some into one that works for all – without turning it into something harmful.

The vaccine

The findings of this study were published in *Nature* last month,[1] and updated findings were presented by principal investigator Louis Picker at AIDS Vaccine 2013 on 8th October.[2]

The RhCMV/SIV vaccine contains sections of the rhesus monkey (Rh) equivalent of HIV, simian immunodeficiency virus (SIV), encapsulated inside the shell of a monkey version of cytomegalovirus (CMV), a near-ubiquitous virus of the herpes family.

Researcher Louis Picker speaking at the AIDS Vaccine 2013 Conference.

It works like a mock infection. The shell of one virus – a *vector* – is used to infect cells with instructions for making proteins that belong to another virus. These SIV proteins, lacking crucial components, can't in themselves cause an infection, any more than a disassembled car can start. But they do alert the immune system so that when the real infection comes along, it is immediately recognised and contained.

The bit of the immune system that vaccines like this engage is the cellular immune system – specifically, the CD8 cells. If CD8 cells can be sensitised by the vaccine,

they will kill off cells infected by the real virus, should it arrive.

This is crucial in the case of HIV because there is a short time window – maybe as short as four hours in receptive anal sex – to stop cells infected in the mucous membranes from taking virus deeper into the body. There they sow their genes into the DNA of long-lived memory cells in the lymph nodes, becoming in the process invisible to the immune system and therefore a chronic infection. (This process seems to take more like four days in vaginal sex, which is one of the reasons it is less efficient at transmitting HIV.)

Unlike a conventional vaccine that stimulates the other, antibody-based, arm of the immune system, a CD8 vaccine won't necessarily completely stop an infection. Instead, it will contain it – corralling off and neutralising the cells subverted by the invading virus.

HIV vaccines stimulating cellular immunity aren't new. But until now their performance in human trials has been disappointing. A previous vaccine that used a viral vector in humans, the STEP trial, may actually have increased some people's vulnerability to HIV.

The exciting aspect of this CMV-based vaccine is that for the first time we have seen a vaccine take action to the point of eliminating infected cells entirely.

The CMV-based vaccine appears to be more powerful because it alerts a different subset of immune cells to previously tried vaccines. These are the 'effector-memory' cells that line the body's membranes and tissues, already on alert for foreign invaders, rather than the central-memory cells that sit deep inside the body, on call but not on patrol.

The other really important difference with the CMV vaccine is that previous vector viruses are eliminated from the body, just as we do with a cold. But CMV, whether as virus or vector, keeps on replicating in the body – and that means the immune response it generates, to itself and HIV, also does not decay.

The trial

A recent report in *Nature* journal[3] about the CMV-based vaccine was picked up by the mainstream press and, as with many recent scientific advances in the HIV field, was hailed as if it was the next step to a cure.

It's not. What happened in this trial is that, in three separate batches, 46 rhesus monkeys were given the RhCMV/SIV vaccine. Then, 13 months later, they were exposed to SIV: 24 male and female monkeys with up to ten weekly shots of virus in the rectum to mimic anal sex, 16 females similarly infected vaginally, and six with up to three direct low-dose injections of SIV to mimic needle sharing. They all acquired SIV, as blood and cellular assays taken soon after infection show.

> “These…proteins, lacking crucial components, can't in themselves cause infection, any more than a disassembled car can start. But they do alert the immune system so that when the real infection comes along, it is immediately recognised and contained.”

The bad news, and the reason this is not 'the cure', is that for 22 (48%) of the monkeys, the vaccine did not work. (By October, 96 had been infected and the vaccine did not work in 48 of them.) They developed SIV infections with high viral loads, including four of the six monkeys infected via injection. That also means they would die within a year or two unless treated with antiretrovirals: the SIV strain chosen is highly pathogenic and typically maintains long-term blood viral loads of a million copies/ml or more. Another reason that this is not 'the cure' is that this is an animal study and, so far, promising signs of success in animal studies have often failed to translate into anything more.

A third reason for more cautious reporting, is that some researchers are concerned that CMV is not safe enough to use in a vaccine for humans; the very fact that it is so active and stimulates such a strong immune response worries people that, through recombination (the so-called 'viral sex' where these little entities swap genes), HIV could reconstruct itself from the vaccine.

The good news is this: the other half of the vaccinated monkeys also became infected with SIV. There was no doubt that SIV was there: as we said above, it showed up in cells. But it was such a pathetic, low-key infection that these monkeys never even made antibodies to the virus – meaning they would test SIV negative. The blood viral load in most of these 24 monkeys was never above five copies/ml, though five showed irregular blips up to 10,000 copies/ml in the first three months after infection but never after (with one crucial exception, which we'll hear more about below).

Five vaccinated monkeys were put down five weeks after being vaccinated so they could be autopsied. They had traces of SIV in 2% of samples of immune tissue (from lymph nodes, spleen, gut, bone marrow and liver). That compares with 100% of samples in an infected but unvaccinated monkey; 16% of samples in a monkey that spontaneously controlled its viral load; and 6% of samples in a monkey on antiretroviral drugs (tenofovir, raltegravir and boosted darunavir).

By excluding the viral protein *vif* from the vaccine, the researchers were able to show that it was immune responses generated by the vaccine, and not ones generated by the virus, that were controlling the infection.

Although strong immune responses to the other proteins were already present at the date of infection – an immune response to *vif* did not reach similar levels till two weeks after infection.

The exciting thing about this vaccine, however, is that even this low-level infection disappeared over time. When **aidsmap.com** first reported on this study two years ago, any trace of viral infection had disappeared in 72% of the monkeys infected rectally a year after infection. Now, three years after infection in the rectally infected monkeys and after at least a year in the monkeys infected vaginally and via injection, blood tests and cell samples could find no trace of virus in *any* of the monkeys that had an undetectable blood viral load. Furthermore, while levels of immune response to the vaccine remained strong, levels of immunity to SIV itself had dwindled to nothing by a year after infection, because by that time there was so little virus around the immune system couldn't sense it.

More stringent tests were done on some monkeys. Even more ultrasensitive assays on six autopsied monkeys found no trace of virus. Three had their CD8 cells depleted by immunosuppressant drugs: no virus reappeared. And finally, in an experiment you could never do in humans, immune cells were transplanted from seven

vaccinated monkeys, two monkeys on ART, and the one 'elite controller' monkey, into ten uninfected monkeys. None of the seven monkeys receiving cells from vaccinated monkeys developed SIV infection; the other three all did.

Ways forward

So this looks like a vaccine that also works like a cure. But why did it only work in half the monkeys? How can we make it work for the other half?

This clearly will be the next crucial research question to answer. One clue we have are the two 'breakthrough' infections. One of the vaccinated monkeys which had been infected rectally, and one vaginally, started developing a detectable SIV viral load several months after infection. In the vaginally-infected monkey it was quite low, typically in the thousand copies/ml range, and was accompanied by a sudden upsurge in her CD8-cell responses to SIV. Essentially she had turned from a monkey whose vaccine was controlling her infection into one whose own body was (imperfectly) controlling it – she'd turned into an elite controller. In the rectally-infected monkey the virus broke through to full infection.

Investigation showed that the breakthrough virus was the same virus the two monkeys were infected with so this was not due to viral resistance.

"Essentially, it's chance," Louis Picker told **aidsmap.com**. "SIV – and HIV – hide in many different places in the body and the patrolling CD8 cells may occasionally miss a place where it is replicating."

Some researchers I spoke to are concerned that a CMV-based vaccine might be risky. "CMV is a live, ongoing infection," said one. "The immune response is strong because it behaves as an actively replicating virus, and whole CMV does cause illness – including AIDS-related conditions – in people with very compromised immune systems."

Louis Picker is more hopeful. He thinks there is something special about CMV – possibly the fact that, evolutionarily speaking, monkeys and humans have lived with it for a long time. It therefore excites a 'Goldilocks' immune response, one that is neither too cold and has no effect, nor too hot and creates illness in itself (most of the symptoms of viruses like flu are due to the body's violent immune response rather than caused by the effects of that particular virus). This means that quite a low dose of the vaccine is protective. There are many other candidate HIV vaccines under study, including other based on members of the same family as CMV. A quick search shows that there are at least eight separate phase 1 (safety and immune-response measuring) vaccine trials going on in England alone at present, and many more worldwide – and those are the ones in humans. One of these may produce sufficiently positive results to be taken forward into a large vaccine efficacy trial sooner than the five years it might take for Picker's vaccine to be developed into a human-adapted vaccine and then given a phase 1 trial – indeed, we hope one does.

There might be other surprises as well as toxicity. Many laboratory animals are interbred and genetically similar. What if the 48% of non-responders were the ones who were genetically different? This would not bode well for a vaccine that would work in the genetically diverse human race.

But this vaccine trial is different from previous trials in some ways. It's not just that it could be a cure as well as a vaccine (though its effect might have to last a very long time to wipe out a chronic infection in a human), it's also that it actually *did* something – eliminated an infection – instead of just generating measurable immune responses.

One of the banes of HIV vaccine development has been the surrogate-marker problem: although our knowledge is improving, we still don't have a set of immune responses we can measure in the body that will unequivocally indicate that a vaccine has a strong chance of working and should be taken forward, and this is only exacerbated in studying different species.

But this vaccine *did* work, albeit in only half the monkeys: and in a way that gives hope not just to people vulnerable to HIV, but those already living with it. nam

Help make history – join a vaccine trial

As we mentioned above, numerous other HIV vaccine approaches are under study, including some human trials in England. Two trials being conducted by Imperial College in London have just been started and are looking for recruits.

In one, three different kinds of vaccine – HIV DNA, HIV proteins wrapped in the shell of another virus called MVA, and an HIV protein called gp140 – are given as injections on two different schedules.

In the other, a vaccine called GTU®-Multi-HIV, which has already been studied as a therapeutic vaccine in people with HIV, will be given as a standard injection or by two novel methods: as a solution applied to the skin and as a vaccine delivered by a method called electroporation, which uses a mild electric shock to open channels in cells so the vaccine can get to where it has an effect more efficiently.

Intrigued? Think you'd like to join a trial? You'll have to be HIV negative (and take a confirmatory test) and between 18 and 45, and fit a number of other criteria.

For more details, including how to apply to join the studies, see **www.helpmakehistory.mrc.ac.uk**.

References

How much longer have I got? [p.3]

1 Farnham PG et al. *Lifetime costs and quality-adjusted life years saved from HIV prevention in the test and treat era*. JAIDS 64(2): early online edition, 1 October 2013.
2 US Social Security actuarial tables: see www.ssa.gov/oact/NOTES/as120/LifeTables_Tbl_10.html#wp1041324
3 May M et al. *Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) study*. BMJ 343, 2011.
4 May M et al. *Life expectancy of HIV-1-positive individuals approaches normal, conditional on response to antiretroviral therapy: UK collaborative HIV cohort study*. Eleventh International Congress on Drug Therapy in HIV Infection, Glasgow, abstract O133, 2012.
5 Sabin C *Review of life expectancy in people with HIV in settings with optimal ART access: what we know and what we don't*. Eleventh International Congress on Drug Therapy in HIV Infection, Glasgow, abstract O131, 2012.
6 Mills EJ *Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda*. Ann Intern Med. 155, 4, 2011.

All change... [p.4]

1 Joint United Nations Programme on HIV/AIDS (UNAIDS) *Global report: UNAIDS report on the global AIDS epidemic 2013*. 2013. Available online at http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf
2 See report on aidsmap.com at: http://bit.ly/19mlqhA

Progress towards an HIV cure [p.12]

1 Henrich T et al. *In depth investigation of peripheral and gut HIV-1 reservoirs, HIV-specific cellular immunity, and host microchimerism following allogeneic hematopoetic stem cell transplantation*. Seventh International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention, Kuala Lumpur, abstract WeLBA05, 2013.
2 Jeffreys R *Sad news regarding attempt to duplicate the cure achieved in Timothy Brown*. TAG blog, 16 July 2013.
3 Persaud D et al. *Functional HIV cure after very early ART of an infected infant*. 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, abstract 48LB, 2013.
4 Sáez-Cirión A et al. *Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy: ANRS VISCONTI study*. PLOS Pathogens, 9(3), 2013.
5 Van Lunzen J et al. *Functional cure after long-term HAART initiated during early HIV infection: a comprehensive case study*. Seventh IAS Conference on HIV Pathogenesis, Treatment and Prevention, abstract TUPE246, Kuala Lumpur, 2013.
6 Martin-Gayo E et al, presenter Yu X. *Cell-intrinsic HIV-1 immune responses in conventional dendritic cells from HIV-1 elite controllers*. Towards an HIV cure symposium, Kuala Lumpur, abstract OA1-3, 2013.
7 Tandon R et al. *Sustained High Levels of Circulating Galectin-9 Despite Viral Suppression among HIV infected Elite Controllers*. Towards an HIV cure symposium, Kuala Lumpur, abstract OA1-4 LB, 2013.
8 Pereyra F et al. *Increased coronary atherosclerosis and immune activation in HIV-1 elite controllers*. AIDS 26:2409, 2012.
9 Chun TW et al. *Rebound of plasma viremia following cessation of antiretroviral therapy despite profoundly low levels of HIV reservoir: implications for eradication*. AIDS 24:2803-2808, 2010.
10 Tolstrup M *Cyclic panobinostat (LBH589) in HIV-1 patients: findings from the CLEAR trial*. Towards an HIV cure symposium, Kuala Lumpur, 2013.
11 Denton PW et al. *Destruction of the residual active HIV-1 reservoir by Env-specific immunotoxin*. Seventh IAS Conference on HIV Pathogenesis, Treatment and Prevention, Kuala Lumpur, abstract TUAA0101, 2013.
12 Moreno-Nieves UY et al. *DC infected by the ANRS MVAHIV vaccine candidate primes NK cells with anti-HIV specific activity through a mechanism involving NKG2D and NKp46 on NK cells and membrane-bound IL-15 on DC*. Seventh IAS Conference on HIV Pathogenesis, Treatment and Prevention, Kuala Lumpur, abstract TUAA0103, 2013.
13 Hansen SG et al. *Immune clearance of highly pathogenic SIV infection*. Nature, early online edition, 2013.

The monkeys' tale [p.16]

1 Hansen SG et al. *Immune clearance of highly pathogenic SIV infection*. Nature, early online edition, 2013.
2 Picker L. *Pre-clinical Development of Cytomegalovirus Vector*. AIDS Vaccine 2013, Barcelona, symposium talk S03.03, 2013.

Keep in touch with the latest HIV news

This is the last printed edition of NAM's regular newsletter *HIV treatment update* – but although *HTU* is coming to an end, there are still lots of ways you can hear about the latest news in HIV.

Daily news reporting

You can read all the news stories posted on NAM's website at **www.aidsmap.com/latest-news**. Our news reporting covers the latest worldwide HIV and AIDS news, including treatment, prevention, and hepatitis and TB co-infections.

You can find news from NAM's own team of writers, plus articles we have selected from other sources. Our news stories report on the latest scientific and medical developments, but we also cover policy and practice from around the world.

We know you value the analysis and comment we include in *HTU* features and we plan to continue publising feature articles online. This will include articles discussing issues in more depth, bringing together experts to debate areas of contention, and interviewing key players in science, medicine, policy making and delivery of care, as well as the people directly affected by what's going on.

And while our online news coverage examines research from around the world, we will continue to keep you up to date on issues of particular interest to people in the UK, such as changes in the NHS and the social and legal environment for people living with HIV.

You can search our online news database, going back to 2001, by topic or date.

You can also sign up to NAM's range of free email bulletins to keep you up to date and in the loop with the latest research, news and developments in HIV.

HIV weekly

A weekly HIV news bulletin, written for people living with HIV in the UK. The bulletin summarises and explains relevant new research and provides links to more detailed articles on our website, aidsmap.com, and news coverage in other media.

You can sign up at **www.aidsmap.com/bulletins** or visit the *HIV weekly* archive at **www.aidsmap.com/hivweekly**

aidsmap news

Sent out twice a month, the aidsmap news bulletin simply highlights all the news headlines recently published on aidsmap.com, as well as news highlights published in other media.

You can sign up at **www.aidsmap.com/bulletins.**

There's an app for that...

We've produced a free HIV news app, available for iPhone and android phones.

The app links to our daily reports on new research, findings and controversies in HIV treatment and prevention from around the world.

Visit **www.aidsmap.com/news-app**

NAM's blog

As well as keeping you up to date with the latest developments in HIV research, we want to keep you up to date with what's happening here at NAM.

We use a blog on our website to let people know about new information resources and tools we produce, any events and webinars we hold, and other things we think you might be interested in hearing about.

Keep an eye on us at **www.aidsmap.com/nam-blog**

Social media

Are you on Facebook or Twitter?

If you use social media websites, we'd love you to connect with us there too.

On Facebook, we are 'NAM – the HIV/AIDS information charity'.

On Twitter, we are **@aidsmap** and there's a feed of our news stories from **@aidsmap_news**.

Conference news

NAM is able to provide you with the most recent scientific and clinical evidence and practice in HIV in part because we report from many of the key conferences covering these and other topics. NAM is the official news provider at:

- International AIDS Conferences
- International AIDS Society Conferences on HIV Pathogenesis, Treatment and Prevention
- European AIDS Conference.

We also report from:

- the Conference on Retroviruses and Opportunistic Infections
- British HIV Association conferences and meetings
- AIDS Impact, an international conference of behavioural and social sciences related to HIV/AIDS prevention, treatment and care
- AIDS Vaccine conferences
- International HIV Social Sciences and Humanities conferences
- International Association of Providers of AIDS Care (IAPAC) evidence summits
- annual meetings of the American Association for the Study of Liver Diseases (AASLD)
- International Liver Congresses

...and others.

You can receive conference e-bulletins, summarising cutting-edge research and other developments, from a range of conferences. Sign up to these at **www.aidsmap.com/conferences.**

Stay in touch!

You may have ideas about topics we could be covering in more detail, or people whose work you'd like to hear more about. We're always interested in your views, so please get in touch with any feedback, or if you'd like to be involved in helping shape HIV information.

Contact us:

- email us at **info@nam.org.uk**
- send us a message via **www.aidsmap.com/contact**
- call us on 020 3242 0820
- write to us at 77A Tradescant Road, London SW8 1XJ

Send us your feedback at: **www.aidsmap.com/Feedback**

nam aidsmap

As we say goodbye to *HIV treatment update*, we wanted to say a big "thank you!" to you – for reading and using it, and for supporting our work.

We'd also like to say thank you for the lovely messages you've been sending in since we announced that this would be the final edition of *HTU*.

"I am glad that [*HTU*] will rise, phoenix like, in a web-based form so I will continue to be kept abreast of the latest developments. Give my congratulations to editors and contributors, past and present, for a well produced and informative publication."

"At times *HTU* has been invaluable to me, has helped me mainly in having informed discussions with medics involved in my care, and leading me to make the right choices for myself."

"I thought that I should say thank you to all those who have kept NAM and *HTU* going over the years... Having a ready round-up of treatment and social news is invaluable and I am sure it has made a difference to many people's lives. I will miss the printed copy."

"I know I have been lucky, but I think I am still alive partly due to making the right decisions at the right times, because I had the information to make those choices and have those conversations...[NAM] gave me tools to make those informed choices."

"You have accompanied me on my journey with HIV, well most of it! Having been diagnosed in the dark days of the early '80s when there was no treatment and very little information available, it was a godsend to start receiving very useful treatment information on a regular basis, especially during a time when my future looked very bleak to say the least, and the doctors were trying me on all sorts of treatment cocktails! Once again, thanks guys from the bottom of my heart. I look forward to accessing the articles on your website."

"I wanted to thank you for the outstanding contribution you have all made in providing accurate information to those living with HIV infection, and equally to all of us in teaching, academic research and patient care who have depended upon *HTU* for ensuring the competence of our knowledge base. The editors of *HTU* have been a remarkable and talented group of experts with a friendly, relevant and hopeful style that has informed and reassured for more than two decades all those affected by HIV. The move to the online publication is terrific and is absolutely the right way forward."

Don't forget to come and see us online! www.aidsmap.com

Thanks to our funders
NAM's treatments information for people living with HIV is provided free thanks to the generosity of:
Abbott; Big Lottery Fund; Boehringer Ingelheim; Bristol-Myers Squibb; Derek Butler Trust; Government of the United Kingdom, Department of Health; Gilead Sciences; Henry Smith Charity; Janssen; M*A*C AIDS Fund; Manchester City Council; Merck Sharp & Dohme; Miss Agnes Hunter's Charitable Trust; NHS Ashton, Leigh & Wigan; NHS Birmingham East and North; NHS Bolton; NHS Brighton & Hove; NHS Manchester; NHS Norfolk; NHS Pan-London HIV Prevention Programme; NHS Salford; NHS South East Essex; NHS South West Essex; NHS West Sussex; Sanofi Pasteur MSD; ViiV Healthcare.

NAM would also like to acknowledge the generous support of its individual donors.

Donate to NAM

Every year NAM provides information resources, like *HIV treatment update*, to thousands of people living with HIV around the world, 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. No matter how big or small, your donation can make a huge difference to the work we are able to achieve. Make a difference today, please donate whatever you can by visiting **www.aidsmap.com/donate** or by calling us on 020 3242 0820. Thank you.

Where to find out more about HIV
Find out more about HIV treatment: NAM's factsheets, booklets, 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 and free web versions of our resources. You can also explore HIV services local to you in our e-atlas, find out more about us in our blog and sign up for free email bulletins.

THT Direct
Offers information and advice to anyone infected, affected or concerned about issues relating to HIV and sexual health.
✆ 0808 802 1221
Mon-Fri, 10am-8pm

i-Base Treatment Phoneline
An HIV treatment phoneline, where you can discuss your issues with a treatment advocate.
✆ 0808 8006 013
Mon-Wed, 12pm-4pm