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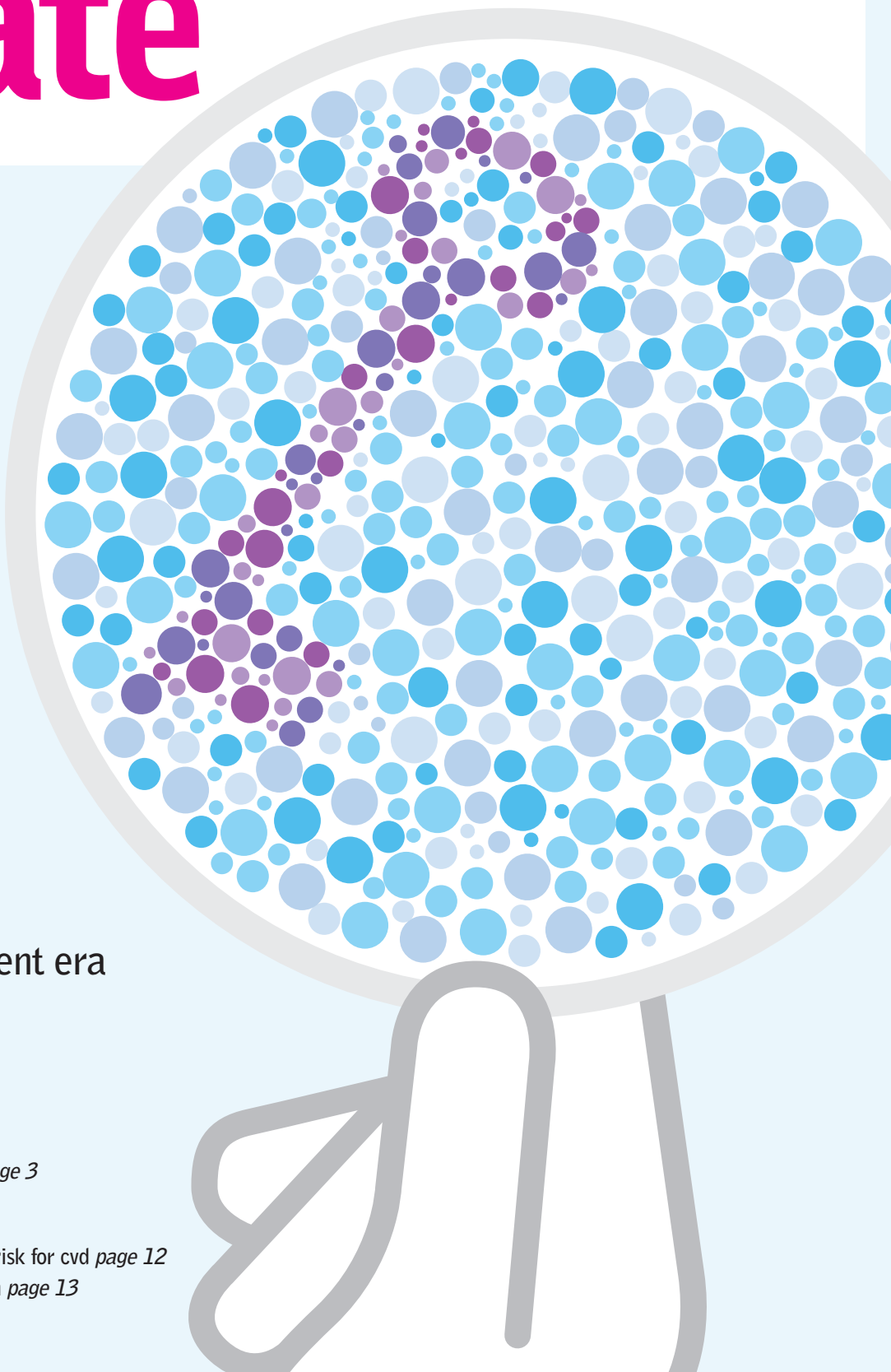
hiv treatment update



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Gus Cairns

in this issue

I'm writing this on a plane on my way to the Conference on Retroviruses and Opportunistic Infections (CROI) in Boston. The annual CROI meetings have been where we've first heard about some of the most important advances in HIV.

First impressions (based purely on the titles of the presentations) suggest we won't see groundbreaking results in treatment or prevention.

Instead it looks as if HIV research, with treatment largely solved, has launched itself aboard a new wave of discovery. The buzz is now about research that could eventually lead to an end to HIV.

We'll hear news of some of the strategies for eradicating HIV that we discuss on page 4. This doesn't mean a cure: the experts interviewed agreed that, as in treatment, a cure is likely to involve a combination of different therapies and procedures.

To expunge HIV from every cell in the body implies technology that makes state-of-the-art cancer drugs look pretty elementary: removing bits of viral DNA with molecular scissors; sending drug-missiles in to seek and destroy the one-in-a-million cells that are infected; assembling and injecting special HIV-proof cells to replace an entire infected immune system.

These are radical procedures and not without risk, but there is a renewed confidence that we will find a way to make them work.

A vaccine to ensure people never *have* to be cured in the first place (see page 14) is just as hard to achieve. Vaccine development hit a low point in 2006 with the failure of one trial, STEP, and many researchers wondered if a vaccine against HIV was impossible.

So when, two years later, a vaccine combination called RV144 turned out to prevent about one-in-three infections, many scientists and activists alike wondered if this glimmer of success might be a mirage, not least because there was no way to explain how the vaccine worked.

Researchers now believe the RV144 effect was real. But finding a truly effective vaccine is like searching for a needle in a haystack of needles. This takes time and money, and researchers and funders are currently arguing about how to develop a more flexible style of trial that produces quicker results without sacrificing credibility.

The third strand of research that stands out at the forthcoming conference is much more practical and hands-on than the high science of cure.

Will putting as many people as possible on treatment really reduce HIV infections? Can we add in other measures (PrEP, circumcision, microbicides) or are they, too, mirages because people won't use them? Does the new 'treatment as prevention' paradigm invalidate old-style safer sex, or will we need to promote it harder than ever?

As Dan Clutterbuck says on page 8, medics and patients are faced with a much more complex set of prevention choices than in the stark old days of AIDS. We all have to be prevention experts now.

At least until they conquer the epidemic, that is.

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

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upfront

Choose your runner

We are absolutely delighted to announce that we have not one, but two, runners in the Virgin London Marathon this year!

This is NAM's first-ever involvement in the marathon. We are proud to introduce you to Janey and Craig, who are bravely taking on the gruelling 26.2 mile challenge to raise money for NAM, and helping us to continue our vital work of supporting people with HIV.

Both our runners have been hard in training since December (yes, in the snow!) and have been determinedly pounding the pavements on a daily basis to get fit, geared up and ready for race day on the 17th April.

Find out a little bit about them below and, if you can, please sponsor Janey or Craig (or both!). And do leave a message of support to assure them that all the long hours of hard work, blisters and cramp will be worth it.

Any donation, no matter how big or small, will make a real difference to the work we do.

Whichever runner you choose to support you can be sure that they are both running towards the same goal, to make the lives of people with HIV longer, healthier and happier.

Thank you.

Visit us online at **www.aidsmap.com/aboutus** to keep up to date with their progress and for photos from the big day!

Name: Janey Sewell

Occupation: Staff nurse in an HIV/GUM clinic

Biggest love: Flowers, gardening and cakes – equally

Biggest fear: Uncomfortable silences

Reasons for running for NAM: I have three reasons: 1. For the people I have referred to NAM in my work 2. To silence my conscience and critics and train for something properly 3. To win (ambitious, I know).

"I often recommend aidsmap.com for people who have tested positive as it's a great source of information. NAM is a charity that I'm excited to be running for!"

Sponsor Janey today at
www.virginmoneygiving.com/JaneySewell

Name: Craig Burrell

Occupation: Sales & Reservations Supervisor at Virgin Limited Edition

Biggest love: Travel - I have been very fortunate and travelled to some fantastic locations all over the world and stayed in some amazing hotels. I also love eating out and trying new restaurants.

Biggest fear: Snakes! I can't even stand seeing them on the TV or in newspapers!

Reasons for running for NAM: HIV could affect every single one of us, no matter what sexuality or nationality. The more people who are aware and educated about it, the better off we all will be in the future.

"NAM is such a great charity to educate and inform people throughout the world regarding HIV/AIDS. It is a great pleasure to be able to raise money for a very worthwhile charity."

Sponsor Craig today at
www.virginmoneygiving.com/CraigBurrell

towards a cure for all: how we might do it

In the second part of this two-part feature, *Gus Cairns* investigates current research into finding a cure for HIV.

Last month, we looked at the case of Timothy Ray Brown, a leukaemia patient who became the first person ever to be cured of HIV infection.[1]

We explained why this is so difficult: even under the most intensive current therapy, a silent 'reservoir' of a type of CD4 cell called 'memory cells' remains infected with HIV. These are like sleeper cells in a resistance organisation – their job is to spring into action when a specific infection they are primed to recognise turns up. In other medical conditions, vaccines work by tricking cells to 'recognise' an infection without actually having had it. The trouble is, when HIV-infected memory cells spring into action, they start spewing out HIV.

We can flush HIV-infected memory cells out of hiding by activating them and then kill them: but the burst of HIV they produce in this process causes more CD4 cells to be infected.

Last month, we explained how Brown's doctor, Gero Hütter, got round this by destroying Brown's CD4 cells and then re-introducing others, via a bone marrow transplant, from a donor naturally resistant to HIV (missing the CCR5 co-receptor, which HIV grabs on to). However, a bone marrow transplant, while the standard second-line treatment for leukaemia, is far too toxic – and expensive – for general use and indeed nearly killed Brown.

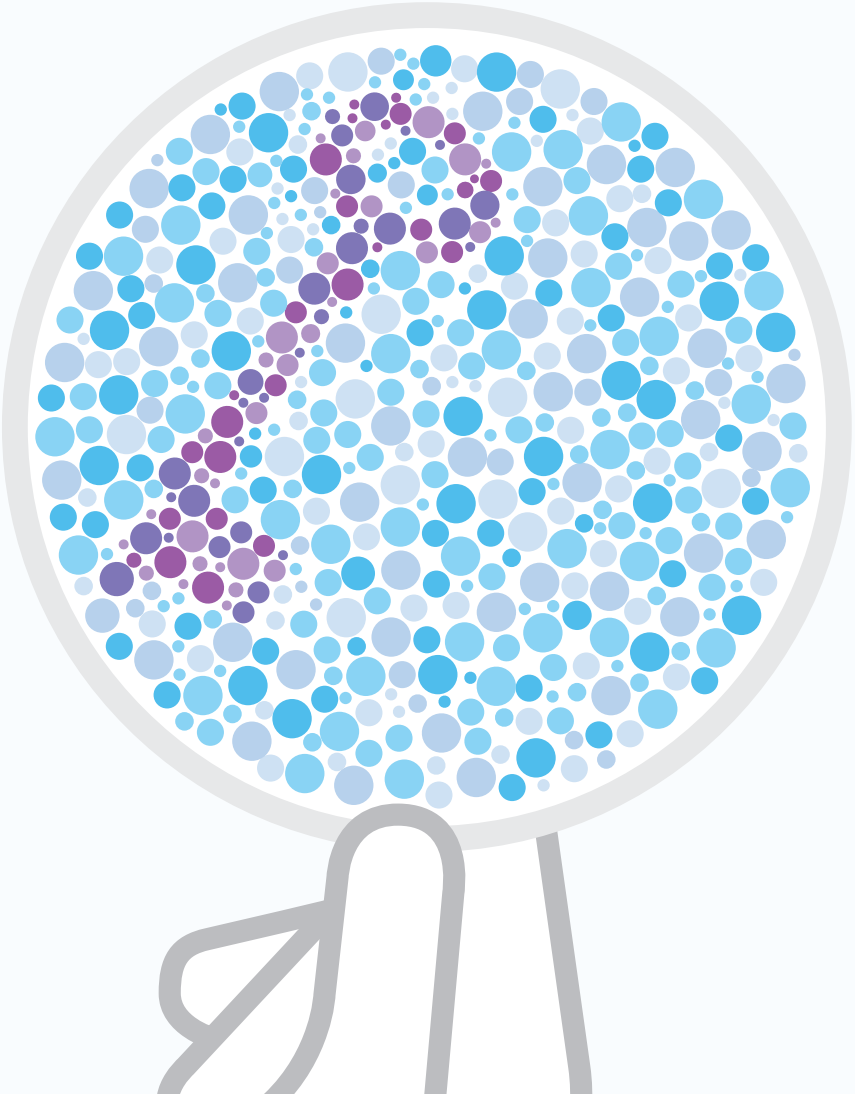
It is, however, proof that a cure is possible. The most promising approach towards a cure for all is to do at least one of the two things Dr Hütter did, but in a much more subtle way.

1. Re-engineer CD4 cells

One approach could be to take bone marrow cells from the patient's own body, and by means of enzymes and genetic tools, engineer them to become CCR5-negative, thus protecting them against further HIV infection. You then re-introduce them into the patient's body, in a so-called 'autologous' – meaning self-donated – transplant.

The hope is that the CCR5-negative cells would slowly start to take over from the CCR5-positive cells and HIV would slowly be starved of the cells it needs in order to reproduce.

Even people on effective antiretrovirals maintain a viral load averaging three copies/ml and this appears to contribute to keeping the immune system in a permanently higher state of activation than in HIV-negative people. This activation kills off some HIV-infected cells but infects others, keeping the reservoir topped up, or so the theory



goes. If, however, a population of infection-proof cells were introduced, they would come to predominate as there would be fewer cells to infect as time went by.

This approach has actually been trialled successfully, in mice genetically modified to be susceptible to HIV. Researcher Paula Cannon and her team from the University of Southern California used a drug called SB728, a so-called zinc finger nuclease enzyme, to snip out CCR5 from mature CD4 cells and then re-introduce them into the blood.[2] They then infected these mice and a control group with HIV. The control mice lost their CD4 cells and developed AIDS within 8 to 12 weeks but the mice given CCR5-negative cells maintained normal CD4 counts and undetectable HIV viral loads.

Many scientists are sceptical that the reservoir of HIV-infected cells could be replaced by HIV-proof cells unaided. The CCR5 cells in Cannon's mice were by no means eliminated, especially the all-important progenitor cells in the bone marrow. Steven Deeks, a prominent cure researcher from the University of California, San Francisco, says: "They did the transplant first and then the infection." It might not work in people already infected, where there is an established reservoir of HIV-infected cells.

Even if it does work, it could take a long time for one cell population to replace another: "In mice it happens in months, in people it could take years," Deeks told *HTU*.

Nonetheless Cannon and her colleague John Zaia are now leading a Phase I trial in patients with lymphoma, using bone marrow transplants of patients' own genetically engineered progenitor cells to try to ensure the growth of a CCR5-negative cell population.[3]

2. Delete infected cells

Alternatively, one approach could be to concentrate more on the immune-destruction part of Timothy Ray Brown's therapy instead of the CCR5-deletion bit. The idea would not be to crudely annihilate all the cells HIV might infect. Instead we could:

- **'Purge'.** This strategy involves enticing reservoir cells out of hiding using drugs that 'switch on' reservoir cells so they become activated and therefore detectable, while keeping patients on antiretrovirals so that the activated cells do not go on to seed new infection. The HIV-infected activated cells would then destroy themselves, and the idea is that repeated cycles of activation would deplete the reservoir beyond the point at which it can replenish HIV – a strategy that's been called 'purge'.

Experiments were done more than five years ago using the drug valproic acid (*Depakote*). This is a member of a class of drugs called HDAC inhibitors, which take the genetic brakes off resting cells. In one study, three out of four subjects given valproic acid achieved a 70% reduction in the number of HIV-infected reservoir cells.[4] It appears, however, that this reduction may only be temporary: two larger studies in 2008 showed no long-term reduction in the number of HIV-infected reservoir cells in other patients.[5,6]

This may be because valproic acid is not strong enough. Trials are planned of a stronger HDAC inhibitor called vorinostat (*Zolinza*), a cancer drug already used for some types of lymphoma and which is being trialled for anal cancer.[7] "Vorinostat is a tremendously powerful drug," says Deeks.

If HDAC inhibitors turn out not to work, there is a second family of drugs called HMT inhibitors, some of them already in use as cancer drugs, that reawaken latently infected cells in a different way. They are only just starting to be studied.[8]

- **'Kill'.** We don't yet know if activating HIV-infected cells would cause so many to commit cellular suicide that HIV would be purged from the body. Instead of enticing cells out of hiding by activating them and seeing if they blow themselves up, how about a more aggressive strategy of directly seeking them out and killing them in their sanctuary sites? Amazingly, attempts to do this date from as long ago as 1988, when a group devised a drug 'missile' that combined an antibody that locked on to the CD4 molecule with a cell-killing toxin derived from the pneumonia bacterium *Pseudomonas*. It wasn't taken further because it wasn't selective enough, targeting all CD4 cells.[9]

By 2002, we were able to make more specific antibodies that only locked on to the memory cells that form the reservoir, and a team devised a similar cell-missile that eliminated a proportion of latently HIV-infected cells in the test tube, from blood taken from patients with HIV. The trouble is that while it cut the number of HIV-infected reservoir cells by at least 80%, it probably didn't eliminate enough, while at the same time picking off rather a lot of non-infected memory cells.[10]

- **'Shock and kill'.** We still don't have a way of infallibly identifying only those one-in-a-million memory cells latently infected with HIV, so we can't kill them and only them. So researchers are devising combination drug missiles that would both entice HIV-infected cells out of hiding and then seek them out actively for destruction. The idea is to devise a three-component therapy that would combine an immune stimulant, an antibody that seeks out activated cells, and a toxin to destroy the targeted cell, a strategy that's been called 'shock and kill'.

One of the possible problems with both 'purge' and 'shock and kill' is that anything strong enough to activate enough immune cells might be too toxic to use – as has already proved to be the case with drugs like IL-2. In particular, some researchers are concerned that it may cause inflammation in places like the brain which may have been what happened to Timothy Ray Brown: an opinion piece warning about this appeared recently in the journal *AIDS*, recommending that attempts to deplete the reservoir this way should be started gradually.[11]

What we really need is a drug that stops cells from being 'latent' and gets them to rejoin the actively circulating, and therefore visible and vulnerable, force of T-cells without widespread immune activation. Researcher Robert Siliciano and his team at Johns Hopkins University in Baltimore are involved in identifying small molecules that could manage this feat, gently teasing the immune cells out of hiding instead of shocking them, and in 2009 identified the first one, a compound called 5HN.[12]

3. Delete resting cells.

Another strategy is to try and find markers that uniquely identify infected

reservoir cells while they are still resting, and kill them without ever having to activate them. Just because we have found no such markers yet does not mean they don't exist. Researcher Rafick-Pierre Sékaly, scientific director of the recently established Vaccine and Gene Therapy Institute of Florida, is investigating possible chemical markers, including an enzyme called PDI (protein disulfide isomerase), which might betray the location of resting HIV-infected cells. Sékaly has identified a multiplicity of active genes that characterise resting cells and appear to keep them quiescent, and has also discovered that the presence of another kind of cell called myeloid dendritic cells may be necessary to keep them that way.[13]

Equally, HIV may gravitate towards cells that display particular kinds of biomarkers already, other than the ones we already know, and we could become able to characterise the subset of cells that is most likely to become infected with HIV and target just those for destruction. The cellular receptors CCR4 and CXCR3 have already been found to characterise immune cells in the gut that are more likely to become infected.[14]

4. Dry up the reservoir

Cells don't just passively stop producing HIV and go into quiescent mode by themselves. The process through which a small minority of CD4 cells join the reservoir of resting memory cells is controlled by a complex chemical pathway whereby specific genes are turned off – just like the lights at bedtime. Instead of trying to prod the resting cells to come out of hiding, we could keep these genes active and stop them ever going into hiding in the first place. Protein disulfide isomerase (PDI) is in a family of enzymes that seem to be involved in this process, but there are many more.

One old favourite is a molecule called nuclear factor kappa B (NFκB), a ubiquitous gene activator that was first investigated as a possible target for HIV drugs 20 years ago. Aspirin is a NFκB inhibitor, though its effect is far too weak and non-specific for HIV therapy. Low levels of NFκB are generated during the low-level viral replication seen in antiretroviral therapy, and these levels appear to help keep the HIV reservoir replenished. If you could find a drug that had a much more specific effect on NFκB or one of the other molecules in the cell suppression/activation pathway, you might be able to stop cells joining the reservoir. Conversely, if you stimulate NFκB or related molecules with a stimulant drug like the plant derivative prostratin,[15] you turn reservoir cells into activated ones – another example of the 'purge' approach.

However, that also illustrates a problem: some of these cellular proteins, like NFκB, do tremendously complex cellular jobs containing many feedback loops. In one situation they are activators, in another, suppressors, and you may find that inhibiting them has the opposite effect to the one you want. Scientists are therefore investigating drugs that inhibit the mechanism whereby the reservoir gets replenished in other ways. Amongst these is a drug called hexamethylene bisacetamide (HMBA) which might be able to stimulate HIV-infected reservoir cells without activating non-infected ones.[16]

Prostratin is quite an exciting drug. This is because, while it stimulates cells to come out of hiding and therefore makes them vulnerable to self-destruction or attack, it also 'downregulates' the CCR5 receptor, and indeed another receptor called CXCR4 which some types of HIV use to get into cells. This means that it could be our best shot yet at a drug that purges infected cells but makes other cells less likely to be infected. Prostratin itself looks rather toxic and until recently, has only been available as an expensive extract from the bark of a tree from Samoa, where it has been used to treat liver disease for centuries. Scientists have recently discovered how to make a cheap synthetic version, which means they can start doing bulk searches of similar molecules to find less toxic drugs of the same type.[17]

The 'combo' cure

We're used to combination therapy against HIV and have more recently started talking about combination prevention. A cure for HIV is also unlikely to involve one 'magic bullet'. Any cure is likely to involve several different approaches, used together or sequentially.

Key players in the search

Gero Hütter,
Charité Hospital, Berlin.

Paula Cannon,
University of Southern California.

Steven Deeks,
University of California, San Francisco.

For instance, we don't yet know if there is a threshold number of infected cells below which active HIV replication is very unlikely to restart. It's like cancer: can we tolerate a few infected cells in the body, or will the presence of even one eventually lead to the return of HIV?

We could therefore use HDAC and NFκB inhibitors to flush out the majority of infected cells, use engineered CCR5-negative cells to try and replace them, and use a therapeutic vaccine to mount continued surveillance against whatever small minority of HIV-infected cells might still remain. Or – since one of the problems with therapeutic vaccination is that it depends on enhancing an immune response, which may lead to more infection – use an immune-suppressant drug to 'lock down' the infected remainder.

There have been a number of attempts already to deliver several HIV eliminators in one package. For instance, the Australian biotech company Benitec has devised a combination consisting of an enzyme that snips out CCR5 from CD4 cells, combined with sections of 'interfering' RNA that delete HIV's reverse transcriptase enzyme and its Tat protein, the viral toxin that over-excites CD4 cells into an HIV-receptive state in the first place. This is all wrapped up in a vector, the shell of an HIV-like virus that infects cells with the genetic products and gets them to start making them. Zaia's team at the City of Hope Hospital in Duarte, California, has already done a Phase I proof-of-concept trial in lymphoma patients in which the genetically modified cells produced the HIV-disabling products for over two years, though only at low levels.[18]

We are only as yet on the first steps of a journey towards making a cure practicable for all, though in researching this article I sensed a new confidence amongst researchers that it might be possible. Many refused to guess at timelines, but Steven Deeks told me that a usable cure strategy would take "at least ten years".

Sharon Lewin of Monash University in Melbourne, Australia, made a keynote address at the opening of the International AIDS Conference in Vienna last year,[19] and, with Nobel Laureate and co-discoverer of HIV, Françoise Barré-Sinoussi, was instrumental in pulling together a pre-conference two-day workshop on strategies towards a cure.[20]

In her keynote address she said she was encouraged by two major cure-research initiatives now underway: amfAR's ARCHE initiative, which had a budget of $1m, and the Martin Delaney Collaboratory, a public/private partnership of research labs funded to the tune of $8.5 million by the US National Institutes of Health and named after the late AIDS activist who founded Project Inform. However, she pointed out that less than 10% of the current funding for an HIV preventive vaccine is currently devoted to curing HIV.

"Cure research doesn't have to be hugely expensive," she told *HTU*. "You don't need the big trials with tens of thousands of people you need for vaccine and biomedical prevention studies. The initial discoveries can be made with studies of 100 people. But we do need large, multidisciplinary consortia like the Martin Delaney project to ensure that research is co-ordinated and not wasteful."

The final question, though, is one only Deeks addressed, among the researchers I talked to. We can control HIV and the illness caused by it, but it's becoming apparent we may never be able to treat everyone because of the massive levels of funding, human resources and healthcare provision needed. Will the same be true of a cure?

"A cure is going to be expensive," he said. "If we were going to do it with aspirin we'd have done it by now. It may also carry with it a degree of risk, and researchers and patients may have to ask themselves how much risk they are prepared to tolerate if the result is going to be elimination of HIV.

"But it's going to be a lot more affordable than lifelong antiretrovirals in resource-rich countries. As to whether it would be scalable for poor countries, though – ah, that's a very different question." ■

Robert Siliciano, Johns Hopkins University, Baltimore.

Sharon Lewin, Monash University, Melbourne, speaking at the AIDS 2010 opening press conference.

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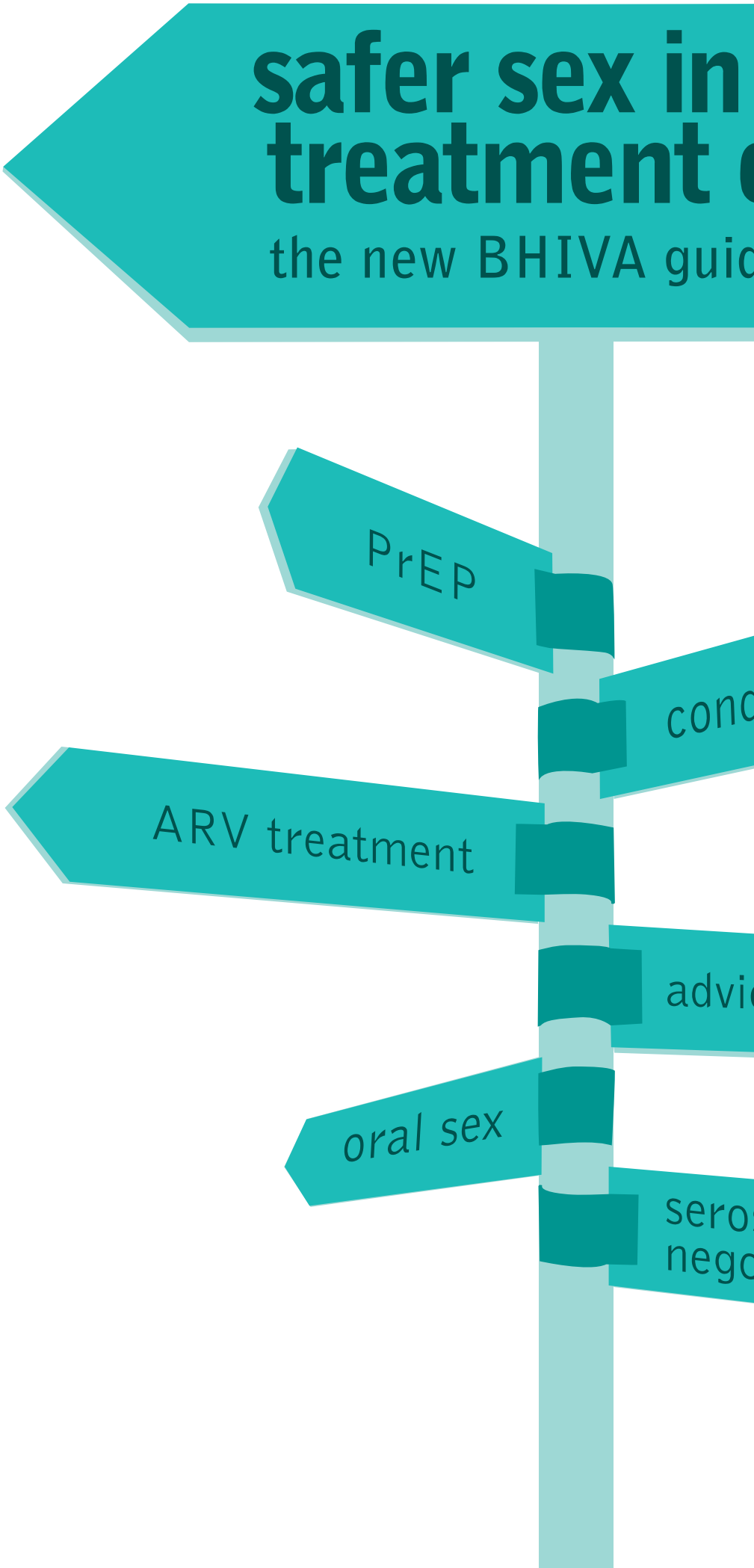
Françoise Barré-Sinoussi, Pasteur Institute, Paris. Nobel Laureate and co-discoverer of HIV.

Wikimedia Commons

safer sex in treatment

the new BHIVA guid

There is mounting evidence that reducing viral load through HIV treatment may be one of the most effective ways of stopping onward transmission of HIV. But how should this influence what we tell patients about prevention? *Dr Dan Clutterbuck*, sexual health consultant in Lothian and the Borders in Scotland and chair of the writing group for the new BHIVA/BASHH safer sex guidelines, explains what they say.



Draft national guidlines on safer sex advice, produced by the British Association for Sexual Health and HIV (BASHH) and the British HIV Association (BHIVA), will be released for general consultation this month.[1]

Advising on safer sex is a routine part of sexual health services, an expected part of encounters between patient and healthcare worker, whether the patient is having a routine check-up for sexually transmitted infections (STIs) or has just been told they have HIV.

The content and format of that advice, though – what to say and how to say it – is much less clearly defined than other aspects of clinical care for people living with, or at risk of, HIV and other STIs.

What to say was simple in the early days of the HIV epidemic: "use a condom". Short of avoiding sex altogether, nothing else worked. Then the UK cut the

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transmission rate from mothers to babies tenfold between 1993 and 1998 by giving HIV-positive pregnant women antiretrovirals (ARVs).

From then on, it was clear that ARVs would play a big role in prevention. How to integrate information on treatment, viral load and infectiousness into more traditional safer-sex advice has been complex ever since, for professionals and patients.

The new guidelines provide advice to healthcare workers on the ways in which this topic might be introduced and managed with clinic attendees and those at risk of HIV infection, formalising the content of advice on avoiding STI and HIV transmission. There is a section providing advice specifically for people with HIV, in a more concise format than existing guidelines.[2] We hope the guidelines will help to ensure consistent advice is given in non-specialist settings as well as in HIV clinics, and to people regardless of HIV status.

Safer-sex advice works

Let's not forget that traditional safer-sex advice works. A review of 18 meta-analyses,[3] each one synthesising results from many studies, found an average increase in condom use of 34% in all the groups studied and a decrease of about 13% in partner numbers. This resulted in an average reduction of 26% in STIs – a spread of different interventions stopped one-in-four STI infections.[4]

It's harder to measure reduction in HIV infections directly: it's a fairly rare event and you need large studies. But one intensive course of intervention in gay men reduced their chances of getting HIV by about one-sixth.[5]

This may be less than you were expecting, though with more intensive support, quite dramatic reductions in risk behaviour have been noted. In the recent iPrEx trial[6] of the antiretroviral drug *Truvada* as a preventive measure against HIV (known as pre-exposure prophylaxis, or PrEP) in men who have sex with men (MSM), for instance, the average number of sexual partners men had in the previous three months went down from 18 at screening, to seven at the start of the study, to just two while on it. Similar results were found in a previous study of PrEP in women.[7]

Safer-sex interventions are an essential element of any HIV prevention strategy, whether in addition to ARVs or in isolation. We don't know, however, what the 'minimum effective dose' is: the effectiveness of a single episode of advice-giving is unclear.

Condoms and treatments

Advice needs to be clear and unambiguous. So the new guidelines contain straightforward, evidence-based recommendations on condom effectiveness, breakage, size and the use of lubricants.

Recommendations on partner reduction, the provision of post-exposure prophylaxis (PEP), and the effect of male circumcision are also included.

One problem is how to turn science into patient-friendly advice for individuals. Areas where lack of evidence makes it difficult to formulate clear statements include the reduction in risk with HIV treatment, the transmission risk attributable to oral sex, and advice on serosorting and negotiated safety (see over).

Initially, the writing group wondered whether to compare the effectiveness of condom use with that of viral load suppression in people with HIV, but decided not to make a direct comparison between the two. Although experts agree condoms are virtually 100% efficacious in preventing HIV if used perfectly,[8] many studies have found that the effectiveness within groups of consistent condom users is around 80%,[9] reflecting the frequency of condom failure and errors in real life.

Evidence for condoms' effectiveness in preventing HIV transmission during sex between men is particularly sparse, although few would doubt that they are highly effective. There is also evidence that 100% use, amongst people at risk of HIV, is quite rare: one study found that only 5.1% of STI clinic attendees used condoms every time they had sex in the year following an STI clinic visit.[10]

In contrast, there is growing evidence for the effect of ARVs in reducing HIV transmission risk. Reports of HIV transmission from people with undetectable plasma (blood) viral loads are confined to a small number of cases.[11,12]

The new guidelines say:

> Taking effective antiretroviral therapy and having a quantitative plasma viral load below the limit of detection of currently available assays significantly reduces the risk of HIV transmission.

The much discussed 'Swiss statement',[13] in which a group of senior HIV doctors in Switzerland said that certain groups of patients on effective HIV treatment "are not" infectious, was clarified after publication to say that transmission risk with undetectable viral load was in fact comparable to that with consistent condom use.

In line with the Swiss statement, the new UK guidelines add that:

> The risks are increased with reduced ART adherence or the presence of STIs in either partner. The risks can be reduced by using condoms and having regular sexual health check ups.

They recognise, though, that couples might consider stopping condom use for various reasons: a long-term monogamous relationship, or planning a pregnancy, for example, but recommend detailed counselling for couples intending to discontinue condom use.

Although there is no evidence yet of widespread behaviour change as people become aware that treatment reduces infectiousness,[14] it is increasingly likely that decisions about disclosure, condom use, and shared responsibility for avoiding transmission will depend on such awareness. These decisions will not always occur within regular relationships, in which extensive counselling is possible.

Greater collective and community understanding of the level of relative risk is needed, both of the uncertainties that apply to the evidence for condoms, and of exactly what we know about viral load suppression. Professionals advising people with HIV or at risk will require increased knowledge and risk literacy, as will their clients.

Although there is currently insufficient evidence to support a blanket public health policy of 'treatment as prevention',[15] starting treatment early to reduce the risk of onward transmission may be appropriate as part of a risk-reduction approach for some people. The guidelines recommend:

> Discussion regarding the early initiation of antiretroviral therapy to reduce the risk of HIV transmission should be considered as part of safer sex counselling for some people living with HIV.

Negotiated safety and serosorting

Alternative risk-reduction strategies are recognised and, where evidence exists for them, included: serosorting, for example, (only having sex, or unprotected sex, with people with your own HIV status). The same thing applied to people whose last test was HIV-negative is often called 'negotiated safety'. We do cite evidence that serosorting may reduce the incidence of new HIV infections in MSM[16] but warn that there may be an increase in other STIs.[17]

The recommendations say:

> Negotiated safety and serosorting should be discussed with those who are known or suspected to be unable or unwilling to maintain 100% condom use. Detailed information and advice should be tailored to the individual's circumstances to maximise the health improvement benefit.

In these areas guidance is potentially contentious; the guidelines go on to add:

> MSM should be advised that serosorting is less effective than consistent condom use but more effective than non-selective non-use in preventing HIV acquisition or transmission.

Oral sex

The guidelines cover other areas of advice too numerous to mention here, but one other potentially hazardous area we enter is to try to give some guidance on the risk of HIV acquisition through oral sex.

Epidemiological evidence on this risk is difficult to verify,[18,19] because few people exclusively have oral sex, but it is regarded as not zero, in untreated individuals at least. Experience and evidence suggests that condom use for oral sex is (very) low in all groups studied.[20,21] Recognising that recommending routine condom use for oral sex is probably unrealistic the draft guideline states:

> Safer sex advice should include information on the risks of oral sex, recognising that individuals must make an informed decision on the level of risk that is acceptable to them, and supporting pragmatic alternative risk reduction techniques.

The guidelines recognise that other STIs are more contagious via oral sex, to the extent of transmission being possible to the genital partner (the one who 'has it done to them') as well as the oral partner (the one who 'does it'):

> The risk of transmission of bacterial and viral STIs including HIV applies to both oral and genital partners, but the risk to the genital partner is thought to be considerably lower. The risks of transmission associated with oral sex are lower than for unprotected vaginal or anal sex except in the case of HSV 1 [the cold sore herpes virus].

The guidelines don't try to resolve the issue of zero or non-zero HIV transmission risk for oral, vaginal or anal sex with people on ARVs with an undetectable viral load, restating that HIV transmission with undetectable viral load is "extremely rare". [11,12]

Commentary

HTU asked some readers what they thought of the guidelines.

Paul Clift, HIV patient representative at King's College Hospital in south London and a member of the BHIVA Guidelines Subcommittee, says:

It really is important that the guidelines emphasise the positive effect of programmes to improve condom use. The effect of this work is often understated. The hard financial cost of one HIV infection, including all expenses incurred, is at least half a million pounds, but because this money is not seen 'up front', it becomes easy for a cost-cutting government or commissioning consortium simply not to spend on necessary prevention.

Dr Clutterbuck's comment that "professionals advising people with HIV or at risk will require increased knowledge and risk literacy, as will their clients." is very important. I hear a lot of confusion about the effect of condoms and of viral suppression in the patients I represent, and I'm concerned that those who are educationally or intellectually capable, and who are Western-orientated in their cultural references, will be able to make this work for them, while those who cannot will be left behind and possibly placed in greater danger of inadvertent onward transmission of HIV and possible criminal charges.

Including patients in writing guidelines would help "turn science into patient-friendly advice for individuals", as BHIVA has done before. A patient representative should be included in necessary further work on translating advice intended for healthcare workers into advice comprehensible to patients.

Silvia Petretti, patient representative on the BHIVA Executive, says:

I have definitely positive feelings about a greater recognition of the role of treatment in reducing risk and the freedom given to serodifferent couples to negotiate levels of risk they feel comfortable with. I do fear though, that as messages around safer sex become more complex, people may feel confused – but over-simplification is patronising. People need appropriate support and counselling to make informed choices, especially as there is a lot of complex information to process and to apply on sexual choices. How this support will be available with the current cuts in the NHS taking place is a cause of anxiety.

I hope the oral sex section will distinguish clearly between vaginal and penile oral sex (cunnilingus and fellatio) because it does often get very confusing.

Ben Cromarty, of North Yorkshire AIDS Action, says:

Although the article says that safer-sex advice works, and goes on to quantify this, I am not so sure that this has been the case over the past decade. The number of HIV and most STI infections acquired in the UK, in both MSM and heterosexuals, has risen steadily, year on year. This suggests that there has been little change in behaviour.

Condom use is a real issue. For some people, the lack of spontaneity is enough to discourage condom use ... comments like "it destroys the moment" are commonplace. For these people – and there are many – even repeated messages about condom use are unlikely to change behaviour. Other risk-avoiding strategies may be used by people with HIV – "I don't come inside him" or "I am now always passive, never active" – in an attempt to minimise risk. Perhaps the most effective message might be (for someone who is HIV-positive) to go onto treatment and maintain an undetectable viral load.

For other folks, though, condom use is no big deal – however, these may by definition be the folks who don't catch STIs and don't go to GUM clinics. When they do turn up, advice given to first-timers at a GUM clinic may need to be much more detailed than that given to someone coming for a routine sexual health screen.

Robert James, patient representative at the Lawson Unit clinic in Brighton, says:

This document is a very impressive one, evaluating the merits of a much wider range of different safer-sex methods than I expected.

The 'safe' option for these guidelines would be to stick to saying 100% condom use and ignore the problems of achieving this. This is particularly so because the Crown Prosecution Service (CPS) has defined reckless sexual behaviour as ignoring "safeguards [that] satisfy medical experts as reasonable". This means, if this is what clinicians advise their patients on safer sex, doing something different could be seen as a sign of reckless sexual behaviour in the eyes of the CPS and make a person liable to prosecution.

Some things do read strangely: partner reduction is recommended for oral sex but not anal or vaginal. Partly this is because of evidence for one and lack of it for another but it does look odd though and implies it is OK to shag lots of people as long as nobody sucks anyone off!

Serosorting for HIV is acknowledged to have an impact, even if nothing like as much as condom use, but increases other STI infections.

The issue of HIV treatment and condoms is probably the only place it feels a little cautious. Treatment alone comes with a caution that it is not always effective, but condom use does not, and the 'Swiss Statement' is posed as a problem, not a solution. I think they bottled out of exploring whether treatment is as good as condoms, rather than whether treatment means people are uninfectious. I do think, though, that in circumstances where using condoms is impossible (e.g. in a violent relationship with someone who refuses) they could have recommended HIV treatment as the best safer-sex method. Such specifics might help some very vulnerable people who could end up in court. ■

What do you think?

The guidelines are draft and open for consultation until 31st May 2011. Feedback is welcomed to ensure that the UK professional and community consensus is appropriately reflected. The final guidelines will be supported by a document detailing the evidence and any new evidence identified in feedback.

www.bhiva.org/safersexadviceconsultation.aspx

news in brief

Hepatitis

Good news on UK hepatitis C rates

About 9% of people with HIV in the UK are co-infected with hepatitis C virus (HCV), a study has found.[1] This is a far lower rate than in other countries, and reflects the fact that, because of the early adoption of needle-exchange programmes in the UK, only a minority of injecting drug users have acquired HIV.

The study, in contrast with a number of European and American studies, found that treatment outcomes for people co-infected with HCV were no worse than for other people with HIV.

It also found, however, that about one-in-five people diagnosed with HIV in the UK have never been tested for HCV, despite guidance that all patients should be screened annually.

Researchers looked at HCV status and treatment outcomes in 31,765 patients attending ten HIV clinics between 1996 and 2007.

Overall, 64% of patients had been tested for hepatitis C at least once. The proportion of patients screened for the virus increased from 9% in 1996 to 80% in 2007.

HCV infection was much higher in patients whose HIV risk factor was injecting drug use. Eighty-four per cent of current or former injecting drug users had hepatitis C compared with 7% of gay men. The investigators suggested some of the infections in gay men may be due to injecting drugs but that patients had either concealed this or they or their doctors had assumed they caught HIV sexually.

Nonetheless, HCV infection was more common in all groups than in the general population, where HCV prevalence is just 0.44%.

Heart disease

Low HDL cholesterol is biggest modifiable risk for CVD

Low levels of so-called 'good' cholesterol are the second-biggest risk factor for cardiovascular disease in HIV-positive patients after age, a recent study has found.[1]

High-density lipoprotein (HDL) is sometimes called 'good' cholesterol as it protects against heart disease. It consists of particles in the blood, which carry fats back from the blood vessels to the liver, where they are stored. In contrast LDL (low-density lipoprotein) is called 'bad' cholesterol as it distributes fats to the blood vessels and raises heart disease risk.

Researchers calculated that the biggest single risk factor for cardiovascular disease in a group of 110 HIV patients was age, which accounted for 41% of the risk, but low HDL cholesterol was responsible for 18% of the risk. This exceeded the amount of risk attributed to smoking (7%), total cholesterol (4%), and male gender (2%).

The average age of this patient group was 37; two-thirds were on HIV therapy, two-thirds were men, and nearly 40% were smokers.

Cholesterol monitoring showed that 3% of individuals had elevated total cholesterol, 5% had high LDL cholesterol and 53% had low HDL cholesterol.

The limitation of this study was that, apart from being small, it was only a snapshot of heart disease risks at one timepoint. A longitudinal study would be needed to follow a larger group of patients and see how many developed heart disease to confirm the low-HDL connection. A number of HIV drugs have been associated with increased risk of strokes and heart attacks and with rises in total and LDL cholesterol. So far the only one that seems to improve HDL levels is the NNRTI drug nevirapine (*Viramune*).[2]

Safer sex

Lubricants may not be safe

Most water-based lubricants used during sex may damage the cells lining the rectum, researchers have found.

The study[1] follows on from two studies presented at last year's International Microbicides Conference (see *HTU* 198). In one, six out of nine lubricants tested were found to damage rectal-lining cells[2] and in the other, people taking part in a microbicide trial who used water-based lubes for anal sex were found to be more likely to acquire chlamydia, gonorrhoea or syphilis than people who did not use them.[3]

Water-based lubes are recommended for use with condoms because oil-based ones weaken the rubber and make them break.

In the latest study, researchers tested 41 commercially available lubes for their toxicity to cells. All were found to be toxic, to a greater or lesser extent, to rectal and colonic cells in the test tube.

Furthermore, four lubes out of the six with the brand name *Astroglide* appeared actively to enhance HIV infection of cultured cells. The researchers found that this was because they contained a substance called polyquaternium-15, which helps HIV attach itself to cells. The least toxic lubricant was the vaginal moisturiser *Replens*.

Condoms are still far more protective against HIV than lubricants are damaging, and not using lube can cause condoms to split. So for the moment, if condoms are your main HIV prevention method, using a water-based lubricant with them is still the safest thing to do.

For coverage of the 18th Conference on Retroviruses and Opportunistic Infections visit **aidsmap.com/croi2011**

However people who for one reason or another do not use condoms might be safer to use non-water-based lubricants. A good compromise is the silicone-based lubricants which, while more expensive, are also condom-friendly.

HPV vaccine

Gardasil vaccine is effective in young men

An international study has found that *Gardasil*, a vaccine against four types of human papillomavirus (HPV) which is already licensed for use in young women, is safe and effective in young men, too.[1]

This study may increase the pressure for *Gardasil* or the other HPV vaccine *Cervarix* to be licensed for use in the EU and given to young men in the UK.

Strains of HPV cause genital and anal warts and the vast majority of cervical and anal cancers, conditions far more common in people with HIV. *Gardasil* provides protection against infection by the two most common wart-causing strains of the virus (HPV 6 and 11) and the two most common cancer-causing strains (16 and 18). In contrast, *Cervarix*, which is currently given to young women in the UK, only protects against types 16 and 18 but may offer significant protection against other cancer-causing types of HPV too.

The study gave *Gardasil* or placebo to 4065 sexually experienced men aged 16 to 26. Fifteen per cent of them were men who had sex with men.

The recommended protective dose of *Gardasil* is three shots over one year. In the 69% of men who took all three shots, only six patients developed genital or anal warts or pre-cancerous conditions. This corresponds to an efficacy against HPV disease of 84%.

The efficacy was higher in heterosexual men (92%) than in gay men (79%), possibly reflecting a higher variety of minority strains of HPV circulating amongst gay men.

Dr Jane Kim, author of an editorial that accompanied the study, said that its results "affirm the potential for HPV vaccines to prevent related disease in boys and men".

Do these results mean that boys should routinely receive a vaccine against human papillomavirus? The data from this study persuaded the US Food and Drug Agency to license *Cervarix* for use in men as well as women. However, anal cancer is much rarer than cervical cancer and only a significant health risk in people with HIV. Some European regulators think that the money spent on vaccinating boys against HPV could be better spent elsewhere, a view echoed by an editorial in the *New England Journal of Medicine*, which published the study.[2]

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what about a vaccine?

There are two ultimate solutions to HIV: a cure and a vaccine. We cover research towards a cure on page 4. But how is the search for an HIV vaccine going? *Gus Cairns* reports.

When HIV was discovered in 1984, the then US Health Secretary Margaret Heckler forecast "a vaccine ready for testing in approximately two years." Years later, we are still nowhere near. Why is it so hard?

Firstly, vaccines work by tricking the body into mounting the immune response it would against a disease. But HIV compromises the body's natural immune response. An HIV vaccine would have to create a response not usually seen.

Secondly, HIV is tremendously genetically variable. A vaccine would have to generate a broad spectrum of responses; in some cases, the virus develops immunity to them.

Three different approaches

Researchers have tried different strategies. One uses a live attenuated vaccine – the basis of many successful vaccines. An actual virus, capable of ongoing reproduction but genetically modified to do no harm, is injected. In animal trials of a live attenuated version of HIV, however, some of the monkeys eventually developed AIDS, because the virus became harmful again.[1] So this strategy was largely abandoned, though some researchers are still investigating it.[2]

The second strategy is to inject bits of the virus to generate an **antibody** response. Antibodies attach themselves to foreign invaders and either destroy them directly, stop them from infecting cells, or flag them for destruction. An effective response could completely protect people against infection. There are tantalising signs that anti-HIV antibodies could do this, but few have been found to have the potency and efficacy needed. We know such antibodies exist – we find rare ones in the blood of some people; when injected into others they block infection. But we don't know how to persuade the body to make them continuously.[3]

The third idea is to use a mock virus – a **vector**. Researchers package up bits of HIV that generate an immune response and put them inside the shell of a different, harmless virus. This smuggles pieces of HIV into immune cells, hoping to generate a memory response and stimulate production of **CD8 cells** or **cytotoxic T-lymphocytes** (CTLs) that kill off HIV-infected cells. This type of vaccine would not necessarily stop infection, but could dampen down HIV replication and render infection harmless.[4]

Three pivotal trials

To prove a vaccine's efficacy, it has to be given to thousands of people. This is partly because the majority would probably not have caught HIV anyway, and partly because we don't have a reliable **'surrogate marker'** – an immune response that tells us the vaccine is working. Because of this, and cost, there have been few large efficacy trials: only three have provided pivotal results.

The first was of a vaccine called **AIDSVAX**. This recruited 5417 volunteers identified as being 'at risk' of HIV. AIDSVAX was a generalised antibody vaccine. It found that the annual infection rate in vaccinated participants was only 2.7% lower than those receiving placebo, nowhere near significant.[5] A similar trial of a different AIDSVAX formulation in Thailand fared no better.[6]

The next big trial, **STEP**, used a CD8 vaccine in volunteers at high risk of HIV infection. Their **ad5 vaccine** consisted of pieces of HIV in the shell of an adenovirus – a type of cold virus.[7]

During the trial, immune responses thought to be protective were seen in volunteers. There was shock, then, when the trial was ended prematurely. The vaccine actually appeared to make some people more vulnerable to HIV.

A 48% higher rate of infection in vaccine recipients was not statistically significant. However, there *was* a significant difference in those with immunity to pre-existing adenovirus infections.[8] It seems that the body 'recognised' the adenovirus in these people and the resulting inflammatory response rendered immune cells more vulnerable to infection.

Expectations were low, then, for the third trial, **RV144**. This was a huge trial in Thailand. Most volunteers were heterosexuals at relatively low risk of HIV. It was controversial because it used the AIDSVAX antibody vaccine, which many scientists considered useless, in combination with ALVAC, a vector vaccine based on canarypox virus.

It was another surprise, then, when it produced a positive result. The group that took at least one dose had 31% fewer infections than those receiving a placebo. This was *just* significantly significant: the 'true' difference in infection rate could have been between 1 and 52%.[9]

Furthermore, the protection seemed to be generated by cells that recognised AIDSVAX and produced antibodies to it – despite that failing in the original trial.[10]

The response generated did look weak. It did not seem to protect volunteers at high risk of HIV and it waned over time: if the study had stopped six months after the first dose, instead of continuing for 3.5 years, the protection rate would have been 60%.

After debate about a possible statistical fluke, most immunologists now accept that the RV144 vaccine did have a real effect – which might be improved. Two studies will start this year: one, RV152, giving 'booster shots' to people who received RV144. In another, yet to start, 125 recipients new to RV144 will get a double dose. A trial using a different vector is also planned.[11]

These will be small studies that can't prove 'real world' efficacy. There are tentative plans for big efficacy trials, but there's no widespread appetite for them, given that there is so much we don't know about RV144.

Because we don't know why some vaccines work and others don't, time-consuming and expensive investigatory trials are still needed. A paper from the International AIDS Vaccine Initiative[12] revealed it takes US$500 million to develop a typical vaccine, but the AIDSVAX and RV144 trials alone cost $235 million.

There is pressure from funders to speed things up. Bill Gates, a major funder of HIV vaccine research, has demanded that researchers "minimise the length of trials and the time between trials".

One strategy being considered is 'adaptive trials': the aims and strategy of your trial change as you go along. You build in criteria for stopping fast if the vaccine looks harmful, ineffective, or even highly effective, and if you anticipated the vaccine would do one thing, but it does another, you change its 'primary endpoint', the main thing it measures.

This is controversial because of the danger of biased results: searching long enough for evidence will probably find some. There are ethical debates too – is it wrong to keep giving a placebo if your vaccine may be working?

The RV144 result has regenerated a degree of low-level excitement in HIV vaccine researchers. We still don't know the way to an HIV vaccine – but there are signs there is one. ■

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