

hiv treatment update

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Gus Cairns

in this issue

Welcome to (sadly) the last monthly issue of *HTU*, or the first quarterly one, according to definition.

We have some meaty and thought-provoking pieces in this issue. Nothing is more complex (and gets people arguing quite so much) than what we should be doing in HIV prevention (see page 8).

As the Health Protection Agency points out, home-grown infections, especially in gay men, remain stubbornly high in the UK. In the last few years we've accumulated evidence that new strategies such as pre-exposure prophylaxis (PrEP), circumcision and the use of HIV treatment as prevention can work – at least in clinical trials. If anything, however, these new options have only served to add to the confusion in the prevention field about the most effective strategy.

Even amongst sensible people who don't think the answer is to ban sex outside (heterosexual) marriage, you get different, passionately held and often diametrically opposing opinions on how to prevent HIV in this country. According to who you talk to, current HIV prevention isn't working and:

- a) it would if we threw enough money at it;
- b) we should stop pussyfooting around and tell people to stop barebacking;
- c) we should forget trying to change people's behaviour and concentrate on diagnosing as many as possible and putting them all on treatment;
- d) we should do c) but add in PrEP for HIV-negative people too.

In reality, we will probably need to combine a number of different approaches: but exactly what

we should combine, using what evidence, in what proportions; how much money we should give each component; and how we'll know if we're doing better are nightmarishly complex questions. How to answer these while spending, preferably, less money is more than enough to tax the brains of NHS commissioners anywhere.

Anal cancer, on the other hand, you might think was a less complex issue (page 4). Squeamish subject, yes, but even if the HPV vaccine isn't going to work for you, surely you can avoid this cancer if you get checked regularly?

The answer is yes, you probably can, but we don't actually know if screening works. And, if it does, we can't show it's cost-effective, which means your HIV or other doctor is unlikely to proactively suggest it. So you have to. Back in the early days of the epidemic, all HIV treatment was like this, because we didn't know what worked.

The issue of anal cancer prevention is, then, surprisingly similar to the one of HIV prevention. The NHS thinks: "We haven't done enough studies and we don't want to waste money on things that aren't going to work." So that leaves it up to the individual, whether that involves demanding an anal screen, demanding PEP, or simply taking responsibility into their own hands and using a condom. Or not having anal sex, despite the shapely butt on this issue's cover. Life's hard, eh?

We're preparing for the International AIDS Society conference now, which we'll report on in the next issue. Have a good summer.

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ISSN 17567890

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charity number 1011220

hiv treatment update

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There is still much work to do

Positively UK's *Silvia Petretti* speaks up at the United Nations.

The UN High Level Meeting on AIDS (HLM) took place in New York in June, to coincide with the 30th anniversary of the recognition of AIDS. It was the third meeting of this kind, previously held in 2001 and 2006. This meeting is important because it establishes the commitment of the UN Member States to addressing the HIV epidemic. The political declarations released in 2001 and 2006 were instrumental in the introduction and scale-up of treatment and prevention across the most affected parts of the world.

As you can imagine, I was extremely excited to represent the Global Network of People Living with HIV (GNP+) at the HLM, and to speak at the closing plenary on the importance of involving people living with HIV in the response to the HIV epidemic. I profoundly believe that our *meaningful* involvement can make this response much more effective. However, during the HLM I started having serious doubts that an institution with so little female representation could devise a political declaration meaningful to women – nearly 52% of the 34 million people who live with HIV worldwide.

During the General Assembly, I watched one male government minister or high-level official after the other making solemn declarations on their commitment to HIV; often they came from countries where I knew women and other affected populations get very little legal or political protection. One of the lowest moments was the panel session on 'Women and Girls', where four out of five panellists were men. I was wondering whether they would ever have a session on men who have sex with men, mostly run by women?

In spite of the under-representation of women in the limelight, women had prepared for the HLM by carrying out a

virtual consultation; Positively UK, the organisation where I work, co-ordinated its European arm. More than 800 women replied to a questionnaire, translated into nine languages and distributed in 95 countries, in just two weeks. This global consultation made clear the wishes of women in regard to HIV:

- Ensure comprehensive and inclusive HIV services that address the visions, life-long needs and rights of women and girls in all our diversity.
- Eliminate stigma and discrimination, and ensure full protection of the human rights of all women and girls, including our sexual and reproductive rights.
- Strengthen, invest in, and champion our leadership and equality to ensure the full and meaningful participation of women and girls, in particular those of us living with and affected by HIV, in the HIV response.
- Empower us to be catalysts of social justice and positive change, and eliminate all forms of violence against us.
- Ensure full access to information and education, including comprehensive sexuality education for all women and girls.

As you can see, women's demands were not surprising or unreasonable.

What seems really shocking is that, firstly, our claims are still not being addressed, and secondly, that in 30 years of AIDS, this was the first global consultation among women supported by UNAIDS and carried out by a partnership of NGOs.

In many ways, the Political Declaration to come out of this HLM is a progressive one. Its most important victories are:

- A commitment to getting 15 million people on treatment by 2015 (80% of the 18 million people who will need it). This is new and a major victory.
- A call on governments to optimise the use of TRIPS (trade agreements)

flexibilities to increase and sustain access to low-cost, generic medicines.

- A target to reduce transmission among people who inject drugs by 2015, including the use of opioid substitution therapy and needle exchange programmes.

But the declaration has several weaknesses, including:

- Only four paragraphs dedicated to women, with the only numeric targets relating to mother-to-child transmission and maternal health: women are only important as 'baby makers'. Our health and prevention needs at all stages of our lives are ignored.
- Transgender people have not been identified as an at-risk population; funds for prevention, treatment and care for this group will still be difficult to obtain.
- Men who have sex with men, people who inject drugs, and sex workers are only referenced in relation to their HIV risks; their human rights are not affirmed in the document. Homophobia, transphobia, and discrimination against sex workers – factors significantly heightening HIV risk – are not mentioned.

I came back from New York sad and angry: there is still much work to do. I am still convinced that unless those of us directly affected by HIV are meaningfully involved, the epidemic will not recede. It is up to us to hold our governments accountable and to continue to demand that our human rights are upheld in policy and in action. ■

🔗 The 2011 Political Declaration (PDF): <http://bit.ly/m1fiY>

Global Survey on Women and HIV: <http://bit.ly/lo61WD>

Silvia's statement to the General Assembly (video): <http://bit.ly/iyGi5A>

Silvia's blog: <http://hivpolicyspeakup.wordpress.com>



everything okay down there? screening for anal cancer

Anal cancer is around 50 times more common in gay men with HIV than it is in the general population. Should we be demanding screening and vaccinations? *Gus Cairns* investigates.

In May 2009, *HTU* wrote about cervical cancer in women with HIV (*Cervical cancer and you, HTU 186*).¹ That article quoted recommendations for “aggressive” annual screening for cervical cell changes, because women with HIV were twice as likely to be infected with the human papillomavirus (HPV), the virus that causes the cancer, three to four times more likely to develop pre-cancerous abnormal cells, and twelve times more likely to get invasive cervical cancer if they do.² If they do get cancer, there is a one in three chance they will be dead of it within ten years.³ But a simple procedure under local anaesthetic can remove pre-cancerous cells if they are identified – and the national screening programme has cut mortality by nearly two-thirds.⁴ And we now have a vaccine against the two most common cancer-causing varieties of HPV, with a programme in the UK to give that vaccine to all teenage girls.

Anal cancer is caused by the same virus and, in the same way as cervical cancer, causes pre-cancerous changes in cells that can be screened for and treated. It’s about 16 times rarer than cervical cancer in the general population. But it’s about 60% more common in women than men and about 50 times more common in gay men with HIV (because anal sex is a risk factor) – which makes it as common in them as cervical cancer is in HIV-positive women and is a huge risk increase: for comparison, lung cancer is ‘only’ 25 times more common in heavy smokers than in non-smokers.⁵ If you do develop anal cancer, there’s a one-in-three chance you’ll die of it within five years.^{6,7}

But, unlike the regular check-ups for cervical cancer in women, there is no standard screening for anal cancer, or even any agreement about whether it would be a good thing. And although the HPV vaccine has been licensed for use in boys in the US, a licence for this use has not been granted in Europe.

Why not? Should we be agitating for better screening – especially of gay men with HIV – for anal cancer and for extending the HPV vaccine to boys?

HPV and anal cancer – the facts

Cervical and anal cancers are caused almost entirely by a viral infection

– HPV – which is not one virus, but a family of about 100 different ones that cause everything from common warts to genital warts to cancers. The majority of sexually active adults eventually acquire at least one variety of HPV and it’s a near-universal infection in people with HIV. For the majority of people HPV has no symptoms.

Only specific varieties of HPV – the so-called ‘high-risk’ types – cause cancers. HPV 16 is the most common as an infection and is associated with the highest rate of progression to cancer. The second most common and aggressive type in the US and Europe is HPV 18. There are at least twelve other high-risk types, some of which are more common than type 18 in other parts of the world but tend to be less aggressive. Types 16 and 18 between them cause 70% of cervical cancers and 80% of anal cancers worldwide.⁸

One important fact about HPV is that, in most cases, the body eventually gets rid of the infection. The average length of any single anal HPV infection is five months to a year in HIV-negative people: people with weaker immune systems may take longer to get rid of it.⁹

Anal cancer differs from cervical cancer in that there is less association between CD4 count and risk, although people with lowered immunity are at greater risk of anal cancer. Most of the increased prevalence is amongst gay men regardless of HIV status.¹⁰ This may be due to more frequent infection with a greater variety of types of HPV, largely due to anal intercourse. HIV therapy is not reducing HPV incidence. A recent French study found that 98% of gay men diagnosed with HIV already had evidence of at least one HPV type, 92% a high-risk type and 43% HPV 16; after two years on HIV therapy these percentages were not significantly lower.¹¹

There are now two HPV vaccines, Merck’s *Gardasil* and GlaxoSmithKline’s *Cervarix*. Both vaccines protect against infection with HPV types 16 and 18, and *Gardasil* against the two most common low-risk genital wart varieties too (HPV 6 and 11).

Testing and grading

The high-risk HPV types tend not to cause obvious genital warts but do cause

changes to the appearance and function of cells in the anal canal, which can be seen under medical examination. Areas either lose all pigment and look white, or get hyperpigmented and look red. While only a tiny proportion of people with HPV will go on to develop cancer, these changes are very common and can be graded by severity. Two grading categories are used, according to the type of medical test done.

In a **smear test**, some cells from the anal region are swabbed off with a sample stick. These cells are suspended in fluid, stained and examined under a microscope, a process called **cytology**. Cells modified by HPV often have larger or multiple nuclei, thicker walls and a generally ‘denser’ appearance.

Cells are graded according to their individual appearance into: normal; ‘atypical squamous cells of undetermined significance’ (**ASCUS**); and low- and high-grade ‘squamous intraepithelial lesion’ (**LSIL** and **HSIL**). If they are fully-fledged cancer cells, but there is no invasive cancer, the diagnosis may be adenocarcinoma in situ (**AIS**).

In an **anoscopy**, the physician will visually examine the anal region in more detail using a proctoscope, and take biopsies: small snips of whole tissue. These will then be examined under the microscope in a process called **histology**, which looks at changes in the whole tissue and how it is organised, rather than at individual cells: for instance, what proportion of cells in the biopsy have become atypical and whether the lesion just affects the epithelium – the surface membrane of the anal tissue – or has penetrated to deeper areas. Any lesions are then graded into anal intraepithelial neoplasia (**AIN**), grades 1, 2 or 3.

Cytology is sensitive – it is good at picking up signs of pre-cancerous changes in cells – but HPV specialists at the Chelsea and Westminster Hospital found that it only correctly predicted the AIN grade in 40% of cases.¹² This is in contrast to cervical cytology in screening, which is over 90% specific.¹³ So, while a smear test may be the cheapest and most convenient way of screening for possible anal cancer, an anoscopy is the only way to decide if changes warrant treatment.

For the types of treatment people can be given, see below.

Screening

Given the comparative rarity of anal cancer, screening the general public is not considered necessary. But for those at higher risk (gay men with HIV, possibly all gay men and women who have anal sex), cervical screening is a good precedent for the value of anal screening. In the UK, cervical screening is offered to women aged 25 to 65. The death rate due to cervical cancer in women under 45 went down by nearly two-thirds between 1988, when screening was introduced, and 2002, despite there being an increase in genital wart diagnoses at the same time.¹⁴

So surely we should be trying to do the same for anal cancer?

Professor Mark Bower is a consultant at London's Chelsea and Westminster Hospital, specialising in HIV-related cancers. Though in favour of people with HIV having regular anal screening, he says that the case for it being routine is surprisingly hard to make.

That's partly because it's still relatively rare. In the Chelsea and Westminster cohort, they have seen 60 cases in 11,112 patients (one per 188 patients) throughout the clinic's history, but this includes patients coming to the hospital specifically to see HPV and anal cancer specialists. In patients attending the Chelsea and Westminster's general HIV clinic, they see fewer than one new case a year.

This may seem odd, given that rates of AIN are very high. For instance, one study of HIV-positive men found that despite AIN grades 2 or 3 being found at least once in 133 of the 247 patients in the study (54%), there were only two cases of anal cancer in three years.¹⁵

We don't know exactly why some anal (or cervical) lesions turn into an invasive cancer, and others don't. Bower has evaluated the cases of nearly 1000 HIV-positive men who have sex with men seen over the last ten years at the Chelsea and Westminster.

"These guys' AIN grade goes up and down and up again," he says. "A lot of

them have been coming here for ten years and show no signs of progressing."

This is partly due to the natural history of HPV and the fact that infections regress as often as they recur. Most AIN grade 1 lesions simply disappear and only a minority progress to higher grades. We don't even know the rate at which high-grade AIN lesions change into anal cancer: estimates vary hugely from 0.2 to 12.5% a year (the consensus is between 1 and 5%). The thing that keeps lesions coming back in gay men is not persistent HPV infection but reinfection; in HIV-positive gay men, persistent infection adds to the risk.

Or incidence of anal cancer may be lower than expected because, in many patient cohorts, gay men with HIV are already being screened regularly. Even in cervical cancer, it has been difficult to calculate the benefit of national screening because so much ad hoc screening was being done before the national programme began.

"Maybe it's because of our excellent interventions," says Bower, "or maybe it's because progression to cancer just doesn't happen in most people with AIN." There has never actually been a randomised controlled trial of cervical cancer screening, and there couldn't ethically be one of an HPV-associated cancer now: would *you* allow your doctor to ignore pre-cancerous cell changes to see if they turned into cancer?

Another problem is cost-effectiveness.

There have been two studies in the US, showing that screening would be relatively cost-effective in both HIV-negative and HIV-positive gay men. In the cost-effectiveness study in HIV-positive gay men, the cost per quality-adjusted life-year (QALY) saved was \$16,000 with annual screening and \$13,000 if done every two years.¹⁶ In HIV-negative gay men, the cost was considerably greater if you screened annually (\$34,800) but comparable if done biennially (\$15,100).¹⁷

However, a UK cost-effectiveness model found that national screening of gay men (with or without HIV) was unlikely to be cost-effective, with an average cost per QALY gained of £39,405, which is

way beyond the usually quoted NICE (National Institute for Health and Clinical Excellence) threshold of £30,000.¹⁸ It was actually more cost-effective to screen all gay men in this study, rather than just the HIV-positive ones.

This model, however, contained a number of different assumptions from the US models. In the US, it was assumed that annual rate of transition from high-grade AIN to anal cancer was high: from 3.6 to 5% a year. Actual surveys suggest a lower rate of progression. The UK study assumed a much lower rate: about one case of anal cancer per 500 cases on untreated AIN grades 2 or 3 (0.2%), or one case per 2500 treated cases. This is probably on the low side, and there have been a number of other criticisms levelled at the UK paper, such as the assumption of a high rate of regression from AIN 1 to asymptomatic.

Screening gay men for anal cancer and its precursors has not been recommended in UK guidelines. The British HIV Association's cancer guidelines of 2008 state: "there is little evidence for routine [screening] as the early detection of lesions still poses substantial difficulties and single biopsies may miss areas of AIN, with histology and cytology yielding some discordant results."¹⁹

In complete contrast, US guidelines – such as those from New York State²⁰ – recommend "anal cytology at baseline and annually", especially for men with HPV or anal warts, and the European AIDS Clinical Society (EACS) guidelines recommend a rectal examination and/or smear every one to three years for gay men.²¹ Anoscopy would be reserved for people with abnormal cytology results, and the New York guidelines estimate that this would be less than 30% of the screened population.

Treatment

One of the reasons screening is not nationally adopted in the UK is because, to quote the BHIVA guidelines, "Treatment options for AIN are limited by morbidity and high recurrence rates." That probably isn't as true as it was. The becoming-standard treatment for AIN is infrared coagulation therapy (ICT), which involves burning off the affected areas

with a heat gun. That sounds very painful, but can be carried out under local anaesthetic, causing only a couple of days' discomfort. High recurrence rates are still a problem: after one treatment, 50% of HIV-negative gay men and 65% of HIV-positive ones had recurrent lesions within ten months. Until we get more data, we don't know if these treatments are preventing progression to cancer – or just subjecting people to unnecessary discomfort.

If you are one of the unlucky few who get anal cancer, it's not the end of the world. With a survival rate of 65% at five years, anal cancer looks bad compared to testicular cancer (97% alive at five years), but very good compared to advanced lung cancer (5% alive at five years). Surgery is not necessary for the majority of people if anal cancer is diagnosed before it becomes invasive. The standard treatment is radiotherapy, plus the anti-cancer drugs mitomycin C and capecitabine, or cisplatin – the kind of drugs that are much more tolerable these days, thanks to anti-emetic drugs.

Less easy to get on with is the radiotherapy, which involves a daily visit to the clinic for six weeks, and causes proctitis (anal and rectal inflammation and pain) for another six weeks or so after that. After these treatments it's the usual watchful wait to see if it's really gone or if it recurs.

About that vaccine...

What about getting yourself vaccinated? And should we be vaccinating adolescent boys as well as girls anyway, in case they get HPV 16 or 18?

In January this year, the US Food and Drug Administration approved the use of *Gardasil* to prevent anal cancer in people (of both sexes) between the ages of 9 and 26. So far, the European Medicines Agency (EMA) has not followed suit. In the decentralised healthcare system of the US, this is by no means a guarantee that your healthcare system will agree to pay for *Gardasil*, but it does mean that people who fall within the age criteria have a fighting chance. In a system like the UK's NHS, EMA approval would only be the first step anyway, as medicines then have to undergo the eagle-eye scrutiny of our health technology

“You should get screened annually and if you're diagnosed with any lesions, you should ask for a referral to a specialist centre like ours.”

**Professor Mark Bower,
Chelsea and
Westminster Hospital**

assessment agency NICE, before the NHS will agree to provide it for free (and, for reasons of cost, the NHS approved *Cervarix* for vaccinating adolescent girls, not *Gardasil*).

The US approval followed a study²² that found that *Gardasil* had 65% efficacy in preventing anal lesions caused by the four types it immunises against in young men aged 19 to 26. That was for all the men who entered the study – and some who were already infected with HPV 16 or 18. The efficacy in men not already infected when they entered the study was 90%.

However, this tells us nothing about whether *Gardasil* really prevents anal cancer or even AIN – because nearly all the anal lesions seen were anal warts caused by types 6 and 11.

If you're older and gay, surely it's too late to vaccinate? Well... not necessarily, because the body can get rid of HPV infections, remember. There is very little research in this area, but a 2009 study largely of gay, HIV-positive, male US Army veterans found that 43% did not have antibodies to HPV types 16 or 18.²³ This could mean they'd just been infected and not yet developed an antibody response, but it could also mean they'd never been infected or had got rid of their infection. An HPV DNA test would tell.

So might you benefit from getting the vaccine? Only if you can find out which

HPV types you have and if you've never had type 16 or 18. In theory the HPV vaccine could protect you from reinfection but we don't know whether it actually does. The vaccine has no effect on current infections. You'll only get it done privately at present and, at £480 for a three-shot course of *Gardasil* (*Cervarix* costs about £315 privately) it is not cheap, and that's not counting the costs of consultation and testing.

Conclusion

So what's a boy to do who is worried about HPV and anal cancer, possibly because he's had anal warts? “You should get screened annually and if you're diagnosed with any lesions, you should ask for a referral to a specialist centre like ours,” is Mark Bower's conclusion. The same would also apply if you are an HIV-positive woman who has anal sex. There's an inevitable contradiction here: while UK cost-effectiveness modellers still come out against anal screening as standard for people with HIV, on an individual level, it is wise to talk to your doctor about getting yourself checked out with a smear test.

You may also want to do a regular self-examination of your anus, although in most cases the lesions caused by high-risk HPV strains tend to be flat and you won't be able to feel anything. But if you do feel anything lumpy, you should certainly have it seen by a doctor as soon as possible. Other symptoms to report promptly are abnormal discharge or bleeding from the anus, itching, pain or pressure around the anus, and anal sores that do not heal. (These symptoms can also be caused by other, more common, problems.)

In a world where HIV therapy is relatively standardised, the mess of contradictory evidence and recommendations around anal cancer thrusts us back to the time when HIV treatment itself was experimental and controversial, and you had to hunt for a hospital that agreed that viral load tests were cost-effective. Keeping yourself safe from anal cancer is one area where patient power makes a difference, and it pays to demand the best service. Get your rear end checked out regularly, and don't die of embarrassment. ■

Gus Cairns finds that UK HIV prevention campaigners and researchers are all in agreement that something has to change. They're not so certain about where we go next, though.

The figures are stark. In much of the world, to quote Michel Sidibé, Executive Director of UNAIDS, "We have halted and begun to reverse the epidemic."¹ But, infections acquired in the UK are increasing, especially so in gay men who, for the first time in more than a decade, were diagnosed in larger numbers than heterosexuals diagnosed here but infected abroad.² Last year, there were more than 3000 new HIV diagnoses in gay men and other men who have sex with men, an 11% increase on the previous year.³

Most other sexually transmitted infections (STIs) are continuing to rise in gay men too, even though – for the first time in ages – the rate is steady or declining overall.⁴ In 2010, gonorrhoea cases were 3% higher in the general population than in 2009 but 33% higher in gay men: gonorrhoea is a good 'indicator disease' for the rate of unprotected casual sex in the population.

Infections among heterosexual people in the UK are also rising, and nearly as fast. But there are still only a third as many and gay men run 50 to 100 times as much risk of HIV as heterosexual people.

This contrasts with the situation in some comparable parts of the world. HIV infections have plummeted in gay men in San Francisco over the last few years,⁵ and more recently there has been a large decline in HIV diagnoses in Washington, DC.⁶ HIV diagnoses have also gone down in British Columbia in Canada.⁷ These declines are attributed in the main to more people getting tested and put on treatment, though people reducing their risk behaviour after diagnosis may be a factor too.^{8,9}

In Europe, there are fewer successes to report, and in some countries with similar epidemics to the UK, such as the Netherlands, infections are also rising.

More choices

What's to be done? There are a number of ways of trying to bring down the HIV

infection rate. Some, such as needle exchange and treating HIV-positive women during pregnancy, do not apply to sexually transmitted HIV. Some, such as post-exposure prophylaxis (PEP), have limited effect at a population level. And some, such as circumcision, may not make a big difference in the UK context where the majority of infections are in gay men (though it might be an option for straight men).

Other methods can be classed as:

- **Traditional:** condom provision plus counselling, support and campaigns to encourage people to have safer sex and use condoms.
- **Promising:** 'treatment as prevention' – increasing the number and frequency of HIV tests and putting as many diagnosed people as possible on treatment.
- **Tested but not tried:** Giving HIV-negative people HIV drugs, as in oral pre-exposure prophylaxis (PrEP) and microbicide gels.

In the last two categories, we have seen some exciting results in the last year or two; scientific trials found that:

- If HIV-positive people were on treatment there were 95% fewer transmissions to their partners (HPTN 052).
- In HIV-negative gay men who took a daily *Truvada* pill, the HIV infection rate was reduced by 43%; in those who reported taking 100% of their pills, this increased to 73% fewer HIV infections (iPrEx).
- In women using a vaginal microbicide gel containing tenofovir, the risk of HIV infection was reduced by 39% (CAPRISA 004).
- A candidate HIV vaccine reduced infections by 31%: not a wild

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Next for prevention?



success, but the first vaccine to show any efficacy in humans (RV144).

- And one important negative result: contrary to the iPrEx trial, oral *Truvada* did not reduce infections in women (FEM-PrEP).

There's any number of ways of responding to these findings. In San Francisco, the public health department has opted to stop nearly all safer-sex campaigns and opted instead to put all the money into maximising testing and treating all people diagnosed, regardless of CD4 count.

In the UK, nothing as bold has been tried yet, although the new guidelines¹⁰ on safer sex about to be published by the British HIV Association (BHIVA) and the British Association for Sexual Health and HIV (BASHH) do take note of the implications of treatment as prevention (see *Safer sex in the treatment era*, HTU 204).

Although there's general agreement that we need to make significant changes to HIV prevention in the UK, we are at the earliest days of agreeing on an effective strategy, which might include some of the above new options in a considered way but which, in the era of flatlined funding, would not require more money to be put in upfront.

A new strategy

Anthony Nardone is a consultant epidemiologist in the HIV/STI department of the Health Protection Agency (HPA), the national surveillance centre for infectious disease. He says:

"We were very disappointed when the 2010 HIV diagnosis figures appeared. Diagnoses in gay men had remained steady for a couple of years at about 2800 and we hoped to start seeing a real HIV treatment dividend; after all, 80% of diagnosed HIV-positive gay men in the UK are on treatment and 95% of those are virally suppressed. It was a sign we had to do something new."

In April, in collaboration with BHIVA and BASHH, the HPA proposed improvements in HIV prevention. We described their embryonic idea in HTU 206 (see *The new prevention*, May 2011). The idea was to roll out a

so-called Intensive Combination Prevention (ICP) programme for gay men at high risk of HIV infection, attending larger genitourinary medicine (GUM) clinics in the UK. The three legs this strategy rested on would be:

1. An intensified system of offers of regular STI screening and HIV testing appointments.
2. Access to web-based health promotion and in-person behavioural interventions.
3. To the highest-risk men, the offer of daily *Truvada* as PrEP, initially only at a handful of clinics.

Have we tried hard enough?

Some people argue we've not been doing traditional HIV prevention properly in the UK, at least not for the last 10 or 15 years, saying we've never practised what's been proven to work and we could promote safer sex a lot better. They're also concerned that the newer, treatment-based approaches to prevention might make matters worse if the focus is taken off condom-based safer sex.

Peter Scott is a member of Status, a new group challenging the way HIV prevention for gay men has been done in the UK. He says that, unlike the US, the UK has only recently started to review the evidence for which traditional prevention methods actually work, and to programme them accordingly. He says:

"I like the ICP idea, and I can see how you could incorporate PrEP as a kind of salvage therapy when other measures have failed. But before you can compare ICP with ICP-plus-PrEP, you need to use the 'combination prevention' that works best. You wouldn't compare a new drug in a trial with one chosen 'because we think it works'. Yet this is essentially how prevention has operated in the UK.

"I recently did some consultancies with HIV agencies and asked them how they *knew* that what they did would lead to fewer cases of HIV. I met a lot of resistance: basically people said 'We're doing what we're doing because it's what we've always done'."

The people who have been providing HIV prevention resources are similarly

cautious about making radical changes like PrEP, but emphasise that as a sector it's been difficult to form consensus about what success in HIV prevention looks like anyway.

Those providing existing HIV prevention programmes are cautiously welcoming of PrEP as part of a wider front of combination prevention.

Ben Tunstall is Terrence Higgins Trust's Head of Health Improvement. He said: "A combination of prevention approaches is the way forward and there must be a backdrop of clear, consistent messaging on HIV and safer sex."

"We need to continue searching for, testing and evaluating new ways to tackle HIV but it's vital we don't throw the baby out with the bath water and drop what we can show is already working. It's not one thing versus another; we need a broad front."

Change needed, but what change?

Others are more sceptical about whether applying safer-sex programmes more rigorously would make a sufficiently big difference to HIV incidence. Sheena McCormack is clinical epidemiologist at the Clinical Trials Unit of the UK Medical Research Council, and a member of BHIVA. She says:

"There is very little robust evidence for behavioural interventions, but in part that's because it's difficult to assess these in a randomised controlled trial. Clearly, behaviour change had a dramatic impact on the epidemic in the period when HIV was a terminal disease, but now that HIV itself is less threatening we need to combine this with other methods."

BHIVA and BASHH have been writing a position statement on what the iPrEx trial implies for the use of PrEP, triggering a much wider discussion on the HPA proposal, PrEP, and the future of HIV prevention in the UK. In the process, the UK PrEP Working eGroup has brought together clinicians, researchers, public health experts, commissioners, prevention promoters and gay and HIV activists, in probably the first attempt in the era of HIV treatment to bring together all UK prevention stakeholders.

Detecting the undiagnosed – and the not-yet-infected

As a result of discussions, a number of important changes were made to the proposed strategy. One set of questions asked from the start was: Who are these 'high-risk' people? Would targeting them be the best way to reduce HIV infections? And how do we go about assessing whether someone falls within this category without stigmatising them or scaring them off?

Dr Martin Fisher represents BASHH in the eGroup. As an HIV clinician in Brighton, he has supported a number of innovative testing programmes.

"We have known for some time that many, if not most, of the new infections are coming from undiagnosed people.¹¹ HPA data indicate that 24% of gay men who test positive have been infected in the last six months, compared with under 10% of heterosexuals. In under-25s that's 35% and up to two years ago it was running at 50% in Brighton. That indicates continued high incidence and fast transmission between networks of gay men.

"So any strategy has to include both reducing the proportion of people already with HIV who are undiagnosed and the length of time they stay undiagnosed, and identifying the people who are most at risk of acquiring it in the next six months.

"There are signs of the beginning of a culture change in HIV testing in gay men – a much higher proportion have been tested at least once – but we need to get far more people testing regularly, as they have managed to do in the US and Australia."

Identifying 'high-risk' people will be crucial to identifying who might benefit from the ICP programme and PrEP, but there is no standardised approach to this in the UK. Sheena McCormack, with others in the eGroup, shares the vision of an online self-assessment tool (tentatively titled *My Risk, My Options*) that could be adopted by GUM clinics and community-based organisations. This would ask people for brief details to create their risk profile for acquiring or transmitting HIV, suggest options available to alter this risk, and recommend resources for more information. For it to work successfully,

they would need to permit the data to be shared with a named professional – probably their GUM consultant. Resources would have to be flexible to reflect what local clinics can offer: for instance, some clinics already offer motivational interviewing-based safer-sex counselling, but most don't.

A trial of PrEP

In the original plan, half the clinics would have offered PrEP to the highest-risk people – basically, gay men having unprotected receptive anal sex. However, feedback from STI clinicians and the eGroup convinced the team that PrEP should still only be offered as part of a clinical trial.

McCormack says: "We don't know whether people will change their behaviour if they know they're getting PrEP."

On the one hand, one of the explanations for the low rates of adherence seen in the iPrEx trial – probably no more than 50% overall – was that people knew there was a 50/50 chance they were taking a placebo. They might be more motivated to take PrEP if they knew they were taking *Truvada*.

On the other hand, if they know they are taking PrEP, will their condom usage plummet, even leading to increased transmission? And if they can't consistently use condoms, will they be able to stick at taking PrEP?

"Only a randomised but open-label trial will answer these questions," says Sheena. "Offering it as part of a trial would also make it possible to offer experimental regimens such as intermittent dosing or taking it only before sex, or before and after sex. In addition, there are regular opportunities to apply for funding for trials, whereas it's not clear where new funds could be found for HIV prevention in the current economic climate."

The idea now is to try to develop *My Risk, My Options* over the next year, while the protocol and funding for the PrEP trial are being confirmed. If successful, it may be possible to use the tool to collect necessary information to complement the public health systems and the trial. The trial's design would randomise participants to an immediate or deferred

offer of PrEP; everyone would be seen in clinic at key intervals for HIV and STI testing, and other services such as established behavioural interventions.

Some big questions

Many more questions remain unanswered about the feasibility of the strategy and the sheer complexity of bringing its different strands together.

One is whether people will use the web-based self-assessment tool. The idea is that anyone presenting for an HIV test would be asked to fill in their initial risk assessment at a terminal at the clinic, but will they continue to do this when they get home? HIV prevention from the last 15 years is littered with the corpses of innovative internet resources for people at risk.

One health promotion worker who works with gay men commented: "Positive people share an interest and will use an online resource, but there isn't really a community of the HIV-negative as such, and it's hard to get them engaged. No one really identifies as a 'risk taker' anyway: denial is a powerful thing."

Not everyone will want to use a self-assessment tool, share the results with their doctor, or have the computer savvy to do so. The challenge, therefore, will be to get community buy-in for this strategy and publicise it widely, which is why involving as big a coalition of stakeholders as possible is important.

Should we restrict the tool and the subsequent offer of PrEP to gay men? Anthony Nardone feels that, for now, we should.

"This is intended to tackle HIV transmission in the highest-risk population in the UK," he says. "To adapt it to other populations would need a larger survey with different questions. It would be great to do that if it works, but right now the cost may not be justified.

"Its other purpose is to gain demographic information in advance of a study of PrEP, and so far we only have proof that oral PrEP works in gay men."

Sheena McCormack feels it would be a waste to restrict *My Risk, My Options* to gay men who turn up with STIs.

"It could be on offer in a whole variety of places," she says, "as the UK's standardised sexual risk-assessment tool. It could be used in a whole number of different settings, by everyone from the 'high risk' to the 'worried well.'" By concentrating solely on gay men, would the programme miss out on detecting the small, but growing, number of highly at-risk heterosexuals?

Why not just put all the resources into testing people for HIV and treating all those diagnosed? This is what happened in San Francisco.

Anthony Nardone says: "Treatment as prevention is very much part of the equation, but if you just concentrate on people who are already HIV-positive you take away the responsibility from HIV-negative people to keep themselves safe, and also the *power* to keep themselves safe.

"If you are someone who is HIV-negative but is highly at-risk – for instance, because you're the receptive partner in anal sex – what's on offer for you? 'Wait till you catch HIV, then we'll treat you' is very disempowering."

Where's the money?

The biggest unanswered question about all this is where the money will come from. The HPA has already had to scale its PrEP ambitions down – though it still aims for about 5000 men to end up being offered PrEP – and GUM clinicians have been telling BHIVA that they couldn't possibly cater for regular six-monthly checks for a high proportion of their patients.

"This is the right time to invest in HIV prevention with new biomedical interventions being added to behavioural ones, but a bad time for the government, and especially the NHS, to have to find new money," says Sheena McCormack. "Over the next year at least, people in the NHS will be preoccupied with the reorganisation, so it seems likely to be a year before any opportunities will arise for new initiatives."

In some ways, this may not be a bad thing: it allows a year's breathing space in which a coalition of prevention stakeholders can formulate a really well-thought-out strategy to hit the funders with.

In other ways, it's a disaster. No one is disagreeing with the HPA's estimate that there will be 100,000 people with HIV in the UK by 2013.

There is one wild card: Lord Fowler, acknowledged as the architect of the UK's original HIV prevention strategy. If he, and the House of Lords committee he is chairing to review the state of HIV in the UK (see Keith Alcorn's piece on page 14), are as shocked with the current state of affairs as the prevention experts, there's a chance the coalition government may reverse the underfunding of HIV prevention. If not, we are set to have one of the highest HIV infection rates in any high-income country, which would impose a crippling cost burden on the NHS.

Martin Fisher ponders: "PrEP and intensive prevention may be cost-effective, but are they affordable?" Equally, in the longer term, will the UK pay the price of not affording them? ■

New from NAM: Preventing HIV



New online on aidsmap is the third edition of *Preventing HIV*, NAM's comprehensive and detailed summary of the history of, and evidence for, methods of preventing HIV ranging from condoms and sexual abstinence to the latest news on microbicides and PrEP (and a summary of the progress towards a vaccine online soon). See www.aidsmap.com/resources/Preventing-HIV/page/1412415/

news in brief



Side-effects

HIV drugs may have caused premature ageing

People with HIV seem to age prematurely. Specific age-associated conditions such as cardiovascular problems and type 2 diabetes are more common in people with HIV; also, more people develop the so-called 'frailty phenotype' early. This is the syndrome experienced in late old age characterised by weakness, weight loss, fatigue, inactivity and falls.

Although HIV drugs were initially implicated in premature ageing, current opinion believes it is associated with HIV infection itself and its long-term immune effects.

Now a new study suggests that some HIV drugs may be implicated after all.¹

Researchers found that people with HIV who have taken some nucleoside reverse transcriptase inhibitor (NRTI) drugs were 20 times more likely to be deficient in a chemical called COX-SDH in their muscles than people who have never taken NRTIs, HIV-positive or negative. The degree of COX-SDH deficiency was strongly related to the time spent taking these NRTIs.

COX-SDH is a marker of muscular strength and the efficiency of the mitochondria, the parts of the cells that provide energy; lack of it implies cells are not functioning normally.

The early HIV drugs d4T, ddI, ddC, and, to a lesser extent, AZT cause mutations in the DNA of mitochondria which means they produce non-functional copies of themselves. Although this study was too small to distinguish between different NRTIs, the NRTIs mainly used these days (3TC, FTC, abacavir and tenofovir) cause little mitochondrial damage.

"An HIV-infected individual treated with NRTIs during their third decade is predicted to develop approximately 5% of COX-deficient cells by age 60," comment the researchers. "This is similar to or exceeds that seen in the healthy very old."

However, not all researchers in ageing agree with the view that genetic damage to the mitochondria is an important cause of ageing. This was a small study and needs to be replicated in larger populations where the researchers can control more carefully for previous medical history and for current health status.

Starting treatment

Small gains in starting therapy with high CD4

An Australian study comparing death rates in patients who started HIV therapy at high CD4 counts (over 650 cells/mm³) has found small but significant reductions in mortality, even compared with starting at the comparatively high figure of 500 cells/mm³.¹

The study recruited 432 patients new to therapy who started with CD4 counts over 350 cells/mm³, and divided them into three groups according to their baseline CD4 count: 350 to 500, 500 to 650, and over 650 cells/mm³. After six years on therapy the average CD4 count in these three groups was statistically the same, namely 689, 746 and 742 cells/mm³ respectively.

However, there was a modest but significant reduction in mortality in those starting at higher CD4 counts. After six years, patients who started therapy at a CD4 count over 650 cells/mm³ were 8% less likely to have died than patients who started at CD4 counts between 350 and 500 cells/mm³, and 4% less likely to have died than patients starting between 500 and 650

cells/mm³. In absolute terms, this means one less death a year in every 3000 and every 6000 patients respectively.

The investigators calculated that, over six years, patients who started therapy when their CD4 counts were over 650 cells/mm³ had a 14% lower chance of developing AIDS or dying than patients starting therapy at between 350 and 500 cells/mm³.

According to the recent HPTN 052 study (see <http://bit.ly/ncGzrm>), putting people on HIV therapy with near-normal CD4 counts at least does them no harm and may even confer clinical benefit. This will add to the debate about whether the prevention benefit of treatment is so great that all people testing HIV-positive should be invited to start therapy on diagnosis.

Testing

One-in-nine new US diagnoses due to expanded testing

An estimated 11% of people infected with HIV in the last three years in the US would not have been diagnosed without routine testing in clinical settings in high-prevalence areas, according to the US Centers for Disease Control (CDC).¹

In 2006 the CDC recommended 'opt-out' HIV testing, in which a test is performed unless specifically declined by the patient, in regions where more than one in 1000 of the local population had HIV. In 2007, it launched the \$111 million Expanded HIV Testing Initiative (EHTI), which targeted 25 districts with high rates of infection in African Americans.

Nearly 2.8 million HIV tests were performed as part of the EHTI between October 2007 and September 2010, yielding 18,432 positive results. The CDC estimates that approximately 56,300 people are infected every

For daily news reports and news selected from other sources, visit: www.aidsmap.com/news

year in the US:² this implies that about 10% of new infections were diagnosed due to the initiative.

One-in-three new diagnoses took place in hospital emergency departments; the rate of positive results here was 0.8%. One-in-five took place in STI clinics and one-in-nine at community venues and organisations. Although community venues only carried out 6% of tests, their positive result rate was almost double that of other settings, indicating the importance of supporting community-based testing.

Hepatitis C

Coffee helps hepatitis C treatment

People with hepatitis C who drink a lot of coffee are nearly twice as likely to be cured after taking treatment, a study has found.¹

People who drank more than three cups of coffee a day were 80% more likely to achieve a sustained virological response (SVR – defined as no detectable virus six months after the end of therapy) than people who drank none.

It is not clear why coffee helps with hepatitis C therapy or whether it will help people who have HIV as well as hepatitis C: this study was only conducted in people with hepatitis C alone.

The study looked at 855 patients who had already taken one course of unsuccessful hepatitis C treatment. Eighty-five per cent of patients said they drank coffee but only 15% had three or more cups each day.

Coffee drinkers had a higher hepatitis C viral load at baseline, but after twelve weeks of therapy, ones who drank three or more cups a day had an average hepatitis C viral load of 100 copies/ml compared to 40,000 copies/ml in non-coffee drinkers.

Over a quarter (26%) of those drinking three or more cups of coffee a day achieved an SVR compared to 11% of those who did not drink coffee.

Side-effects

Abacavir heart attack risk still unclear

Studies in Denmark and amongst US forces personnel have produced contradictory findings on whether the NRTI drug abacavir (*Ziagen* – also in *Kivexa*) is associated with heart attacks and strokes.

The apparent link between abacavir and cardiovascular events was first uncovered by the D:A:D cohort study in 2008.¹ Other studies, however, have failed to find a link.²

The Danish study³ looked at 5031 people accessing HIV care and contrasted their risk of having a stroke or other cerebrovascular event with the risk in 45,279 people in the general population. In this study, people taking abacavir were 66% more likely to have a cerebrovascular event.

However, a study by the Veteran's Administration in the USA,⁴ following over 19,000 patients who received care between 1994 and 2004, while finding initially a slightly raised risk of heart attack in people taking abacavir, found that this increase may also be explained by kidney disease, a known risk factor for heart attacks.

Patients taking abacavir were 27% more likely to have hearts attacks than average, but they were also 25% more likely to have kidney disease than patients taking tenofovir.

Because tenofovir can cause kidney failure, mainly in people with pre-existing disease, people with kidney problems are both more likely to have heart attacks and to be prescribed abacavir.

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talking to the lords

Keith Alcorn, NAM's Senior Editor, recently testified to the House of Lords Select Committee on HIV and AIDS in the UK. He hopes their Lordships can exert some pressure to revitalise HIV policy after its years on the sidelines.

We all know that the British response to HIV has been left to slide in recent years. Although we have some of the best standards of treatment and care in the world, our record on prevention is unimpressive, to say the least. Indeed, the previous government largely ignored the issue.

Today, politicians – including government ministers – are realising the extent of the mistake.

At the end of 2010, the House of Lords established a Select Committee to investigate the state of the HIV response in the United Kingdom. It was set up at the urging of Lord Fowler, responsible for the 'tombstone' HIV prevention campaign of the 1980s, but also for the enlightened and pragmatic way a Conservative government set about dealing with thorny issues such as needle exchanges and talking about sex in public.

Time-limited parliamentary committees like this one don't scrutinise proposed legislation. Instead, they scrutinise areas of concern and make recommendations to government.

Recommendations from a committee led by a high-profile peer will create

attention and influence, especially when getting value for money on health is at the centre of national politics. While some committee reports sink without trace, this one is likely to coincide with intense restructuring in the HIV sector, and in the way that HIV treatment and prevention are organised and funded.

I was invited to give evidence to this Select Committee on how the NHS can best commission and deliver HIV treatment.

Although parliamentary Select Committees often look like the Spanish Inquisition, this Committee was less interested in scoring points and more interested in hearing from a wide range of experts. In particular, the Committee wanted to know where treatment could be delivered most effectively.

At the time of the hearing, it had just been announced that HIV care would stay with a strategic commissioning body, rather than being devolved to individual GP consortia like most other conditions. A national body will have an overview of how HIV care will be delivered in the UK, at least in the short to medium term.

However, there was interest in the extent to which HIV care could be delivered through general practitioners. I felt it was particularly important to get across two points.

The first was that the needs of people with HIV in the UK continue to be complex; it would be a mistake to assume that everyone will eventually be cared for through GPs.

Although care delivery needs to be redesigned as HIV treatment evolves, ripping up the current system of commissioning and delivering health care without recognising its strengths would be a disaster.

Management of patients with uncomplicated HIV infection may in the longer term be suitable for devolution from hospitals to general practice or to polyclinic-type centres, where district clinical nurse specialists can deliver HIV clinics. Innovations in monitoring technologies and information technology, coupled with greater durability of HIV treatment, mean that most people who start HIV treatment without any symptoms might rarely have to attend a hospital for care after initial work-up.

Secondly, new technologies allowing self-monitoring of a condition, and delivery of drugs to home or work, will reduce patients' future need for interaction with general practice. With good patient information and a supportive healthcare system, many people with HIV will be able to take greater responsibility for self-management of their condition.

However, it is overly simplistic to assume that most patients with HIV will eventually be managed through general practice, with high levels of self-care. A recent study projects that, in 2013, 50% of people with HIV receiving care



in the UK (39,000 people) will be classified as symptomatic or AIDS-diagnosed.¹ This refers to the stage when someone was diagnosed and indicates their subsequent use of hospital services. There is extensive evidence that late diagnosis with symptomatic disease is strongly associated with a higher risk of developing co-morbidities such as cancers, osteoporosis, cognitive impairment and kidney disease.

There will be a need for continued strong linkages between local HIV care and expertise at centres of excellence, with a strong case for concentrating specialist care at a smaller number of major centres. There will be a growing need for collaborative working between HIV services and other specialisms such as cardiovascular medicine, oncology, hepatology and geriatric medicine as the HIV-positive population ages.

Effective commissioning must recognise that the long-term needs of the HIV-positive population will remain complex, possibly for most, requiring care networks within a national or regional framework.

GP commissioning would undermine the evolution of HIV services towards a network model, isolating aspects of care and setting up contractual barriers to collaboration between those with the greatest expertise in managing complex cases – those cases with the greatest potential to incur costs to the NHS. Research shows the average inpatient days for patients with AIDS rose from 7.7 per annum in 1997 to 10.9 in 2006, despite a decline in new AIDS diagnoses,² indicating the growing complexity of care and ageing of the HIV-positive population.

The Government's White Paper *Equity and excellence: Liberating the NHS* has undertaken to put information for patients at the heart of the NHS. The management of increasingly complex conditions requires a continued focus on high-quality patient information to help patients navigate healthcare systems and engage in effective self-care.

Prevention

The Committee has also heard very clear evidence from the Health Protection Agency (HPA) that the

biggest priority for prevention in the UK needs to be gay men.

"We are advocating a substantial increase in the intensity of testing in the gay community," Professor Noel Gill of the HPA told the Committee. He said that the continuing high rate of new infections among gay men needed to be tackled by Intensive Combination Prevention (ICP, see *Where next for HIV prevention?* on page 8), built around the GUM clinic network.

There was considerable disagreement in the evidence given to the Committee on the current state of HIV prevention in the UK. A minority of witnesses and submissions were highly critical of current HIV prevention messages targeting gay men, criticising them for appearing to condone sex without condoms.

Most witnesses stressed another problem: the sheer lack of scale. Despite a lifetime treatment cost of around £285,000 per infection, the HPA estimates that only 3% of the entire NHS funding allocated to HIV is spent on prevention.

The Committee returned again and again to this problem, and it seems likely that it will make a strong recommendation that more money needs to be devoted to HIV prevention in the UK. It was highly critical of current levels of spending during an exchange with Health Minister Anne Milton, who refused to give any indication that current efforts could be improved if a bit more money could be spent. But then what else would a government minister say?

Unfortunately, it is clear that one thing that excites the Committee is the idea of another national campaign like the 'tombstone' campaign of the 1980s. Milton expressed scepticism about this approach, and it would divert attention away from the bigger issue of how we increase the scale and effectiveness of prevention, but don't be surprised if it's a headline recommendation.

The Committee is due to report its conclusions by the end of July, and I predict this will kick off a period of intense scrutiny of the way in which HIV prevention and treatment are organised in the UK. ■

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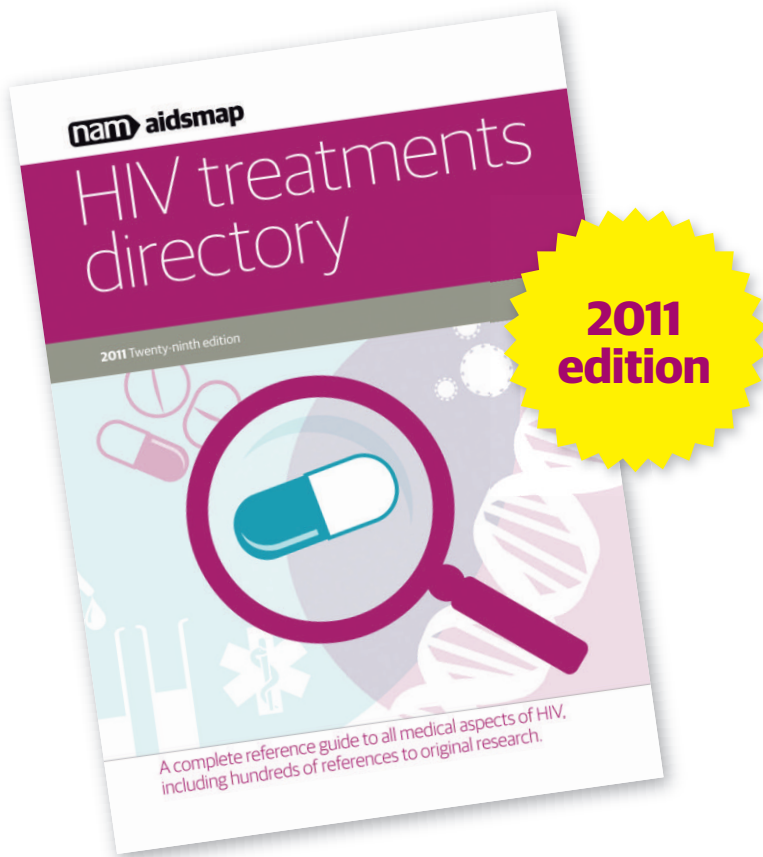
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 Merck Sharp & Dohme;
 Miss Agnes Hunter's Charitable Trust;
 NHS Ashton, Leigh & Wigan;
 NHS Birmingham East and North;
 NHS Bolton;
 NHS Brighton & Hove;
 NHS Manchester;
 NHS Norfolk;
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