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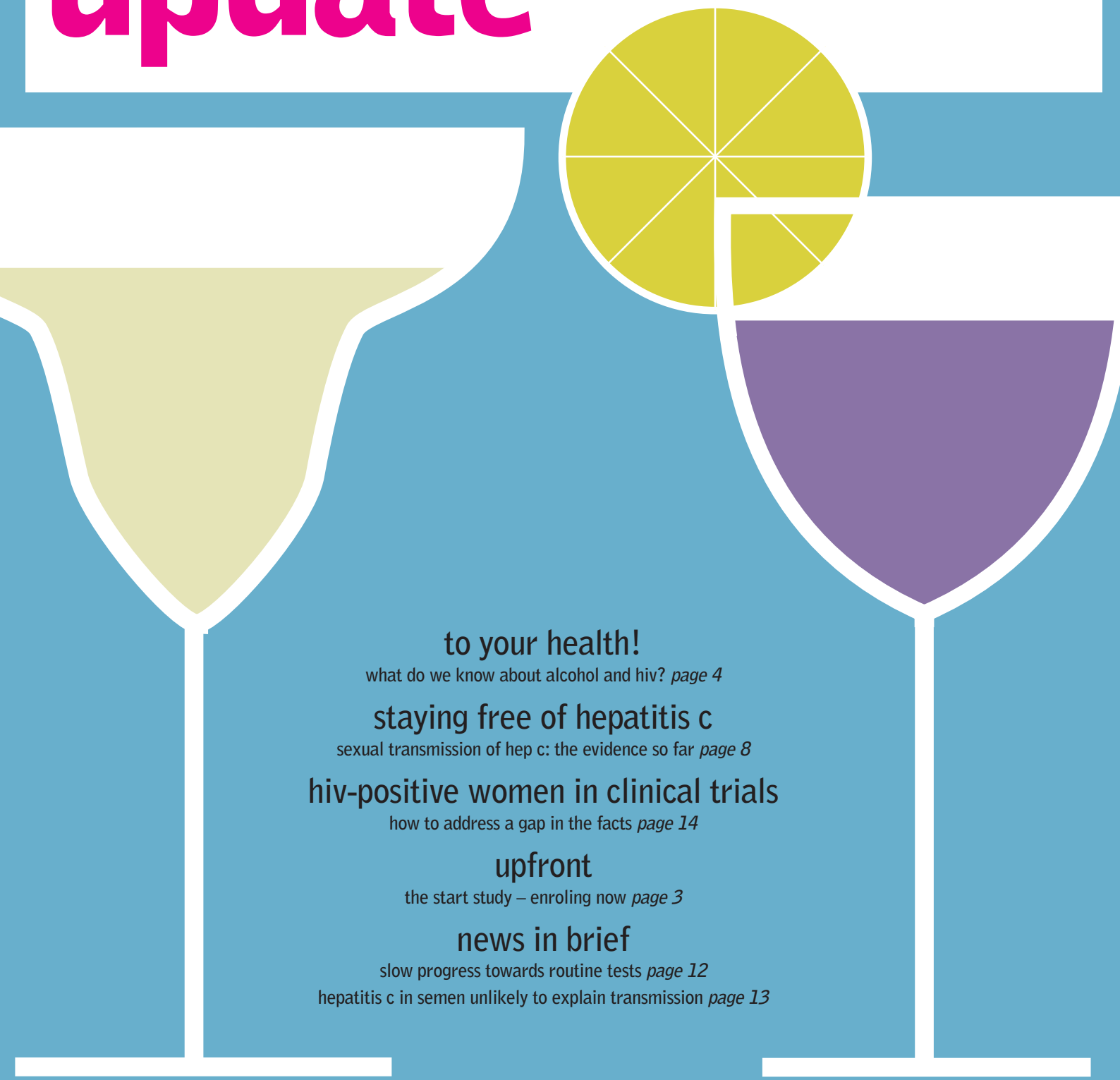
www.aidsmap.com
issue 197 june 2010

hiv treatment update



Gus Cairns

in this issue

There's probably no dafter saying than "What you don't know can't hurt you". Not one you'd expect us to agree with, given that NAM's whole raison d'être is to arm people with the information they need to make the best health decisions.

Not that we always do make the best decisions for our health, of course. Liz Highleyman's piece (*To your health!*, page 4) reminds us that drinking more than about a pint of beer or a large glass of wine a day is likely to do your health more harm than good. People don't always pay attention to messages like that because, well, having a life is as important as living. But at least if you know it, you can balance your body's needs against your social need for a pub night.

Unfairly, women have less tolerance to alcohol than men, and those who like more than the odd bevvy may be storing up liver trouble for the future. We don't know if that's especially the case for women with HIV. Indeed, as Sharon Walmsley says on page 14, there's an awful lot we don't know about HIV-positive women's health in general, because for far too long researchers have been treating women as if they were an alien species.

That was understandable – if regrettable – when women formed a small minority of HIV-positive people. But now, when even in a country like the UK nearly 40% of people with HIV are female, there's really no excuse for researchers and drug companies not to include women in significant number in clinical trials.

Another thing we don't know enough about (and something you don't want if you like a drink) is hepatitis C; specifically, how it's really being transmitted in the gay men becoming infected (*Staying free of hepatitis C*, page 8). There's an urgent need to find out more because until then, we don't know what our advice to gay men should be. Is it about the sex you have – or the HIV you have?

This is quite political, because there's a risk of assuming hepatitis C is the result of 'bad behaviour' and stigmatising the men who catch it, when it may be having HIV itself that makes people so much more susceptible. That mistake was made once before in the early '80s when AIDS was blamed on the behaviour rather than a virus. Let's not do it again.

There's still an awful lot we don't know about HIV. That's why the START trial is so important, as Simon Collins says opposite.

We need to find out if everyone should be on HIV drugs from the word go or if that's going to do more harm than good in people with high CD4 counts. It's odd that some HIV organisations and clinicians are acting as if we know this already – we don't. START is also important because if 'treat everyone' turns out to be a bad idea, it would stymie prevention campaigns that rely on reducing viral load.

Without that knowledge we might do more harm than good, whatever decision we make. So, as PhD students always end up saying: "more research is needed".

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

charity number 1011220

hiv treatment update was founded by Peter Scott

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

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upfront

START – and why the time is now?

Simon Collins of HIV i-Base looks at an important and exciting new study, which needs your help

The START study (Strategic Timing of Antiretroviral Therapy) is exploring when to start treatment and many other aspects of HIV.

Despite 25 years of research, there has never been a randomised study looking at the best time to start treatment. START is important because it is randomised. This is not just a technical point. It means that the results will be accurate and real. Nearly all the current evidence for starting treatment is based on studies where other factors can affect the results, and which do not measure risks.

START will help show the differences between starting at 350, 500, 900 or at even higher CD4 counts. It will help us understand how HIV affects our brain, our bones and our heart, whether earlier treatment helps, and how genetics, treatment and ageing interact with HIV.

START has generated a lot of discussion because the US Department of Health and Human Services guidelines[1] recently changed the recommended CD4 count for starting HIV therapy from 350 to 500 cells/mm^3. But this was based on limited evidence – mainly graded as expert opinion.

Their reasons were that we now have safer and more tolerable drugs, that untreated HIV causes other health complications, and that having more people with undetectable viral loads will reduce transmission. But defining exactly when the benefits of treatment outweigh the risks is not clear.

Some of the US experts recommended treating people before their CD4 count falls below 500 cells/mm^3 too. They were not saying, 'we don't need the START study' but that rather, while waiting for results, they prefer to recommend treatment.

Others think this issue is far from clear. A community statement[2] to the US guidelines panel signed by over 150 organisations, including i-Base and NAM, supported the importance of START in order to study what happens if people start treatment with CD4 counts between 350 and 500 cells/mm^3. Guidelines in the UK and European countries still recommend not starting treatment till the CD4 count is below 350 cells/mm^3 unless there are other considerations.

Why not just treat everyone anyway? If HIV treatment had no side-effects and was robust, effective, cheap, not prone to resistance or needing high adherence, everyone could start treatment with their HIV-positive test result. But, good as it is, it doesn't score highly on all of these factors.

There is good evidence for treating once your CD4 count has dropped below 200 cells/mm^3, and for treating everyone below 350 cells/mm^3 if there is access to modern treatment. But current research suggests only small absolute benefits at higher CD4 counts, when there is only a small chance of any HIV-related health complication. Opinions may be strong both for and against treatment above 350 cells/mm^3, but the evidence is weak.

To take part in START, you need to have a CD4 count over 500 cells/mm^3 without being on treatment, and be currently well. Participants are randomised to either start HIV treatment immediately (at any CD4 count) or wait until their CD4 count drops to around 350 cells/mm^3.

Deciding to take part in a clinical study is an individual choice. You have to be happy to use either strategy, because you will be randomised to one or the other. Currently, while most doctors might personally guess one option might be better, they generally agree that the evidence for either position is limited.

Only about 10% of people are diagnosed with CD4 counts over 500 cells/mm^3, and only 10% of people stay above that level for many years without treatment. So finding people to join is a challenge. If you were recently diagnosed, you may need time to come to terms with your diagnosis before starting treatment, but looking into the benefits of early treatment is where some of the most exciting research is currently happening. If you have been controlling HIV well for several years without treatment, there is increasing evidence suggesting that even 'long-term slow progressors' could be at risk if they defer treatment for many years.

If you choose to take part, as well as getting great care and the chance for monitoring not generally available in clinics, you can contribute to important research.

Simon Collins is a member of the Community Advisory Board of the INSIGHT Network, which runs the START trial.

START sites include the Chelsea and Westminster, Royal Free and St Mary's hospitals in London, and in Brighton and Leicester. If you are treated elsewhere, you will need to initially visit one of these centres, but travel costs can be reimbursed.

For more details and to contact the researchers see:
http://i-base.info/home/start-study/
or contact START@ctu.mrc.ac.uk

i-Base phoneline: 0808 800 6013.

to your health!

Liz Highleyman investigates the research to date on alcohol and HIV.

Most people can drink alcohol with few or no ill effects, but if used unwisely it can be a major cause of health and social problems, ranging from liver cirrhosis to road accidents. In fact, alcohol causes more deaths in the UK – more than 9000 in 2008 – than any other drug except tobacco.

There is little evidence that light or occasional drinking is a major concern for most people with HIV. But alcohol has been linked to increased risk of HIV transmission, and it can contribute to poor adherence to antiretroviral therapy.

Who drinks?

By country, the UK has the eighth-highest alcohol consumption in the world[1]: men drink about 15 units per week on average, whilst women drink ten units.[2] A unit is defined as 10ml or 8g of pure alcohol.

That's less than you might think: half a small (175ml) glass of wine, a third of a pint of beer (at 5 or 6% alcohol, as many lagers typically are now), or a single pub measure of spirits. The NHS recommends that men should not exceed three to four units per day on a regular basis and women should not exceed two to three units per day on a regular basis. That's, respectively, about a pint of beer or a medium glass of wine a day – not what a lot of people think of as excessive.

Heavy alcohol use and binge drinking, or consuming a large amount at one time, are common. A recent study in Chester, Liverpool and Manchester found that one in seven men and one in 25 women said they intended to consume more than 40 units (equivalent to about twelve pints of beer) during their evening out.[3]

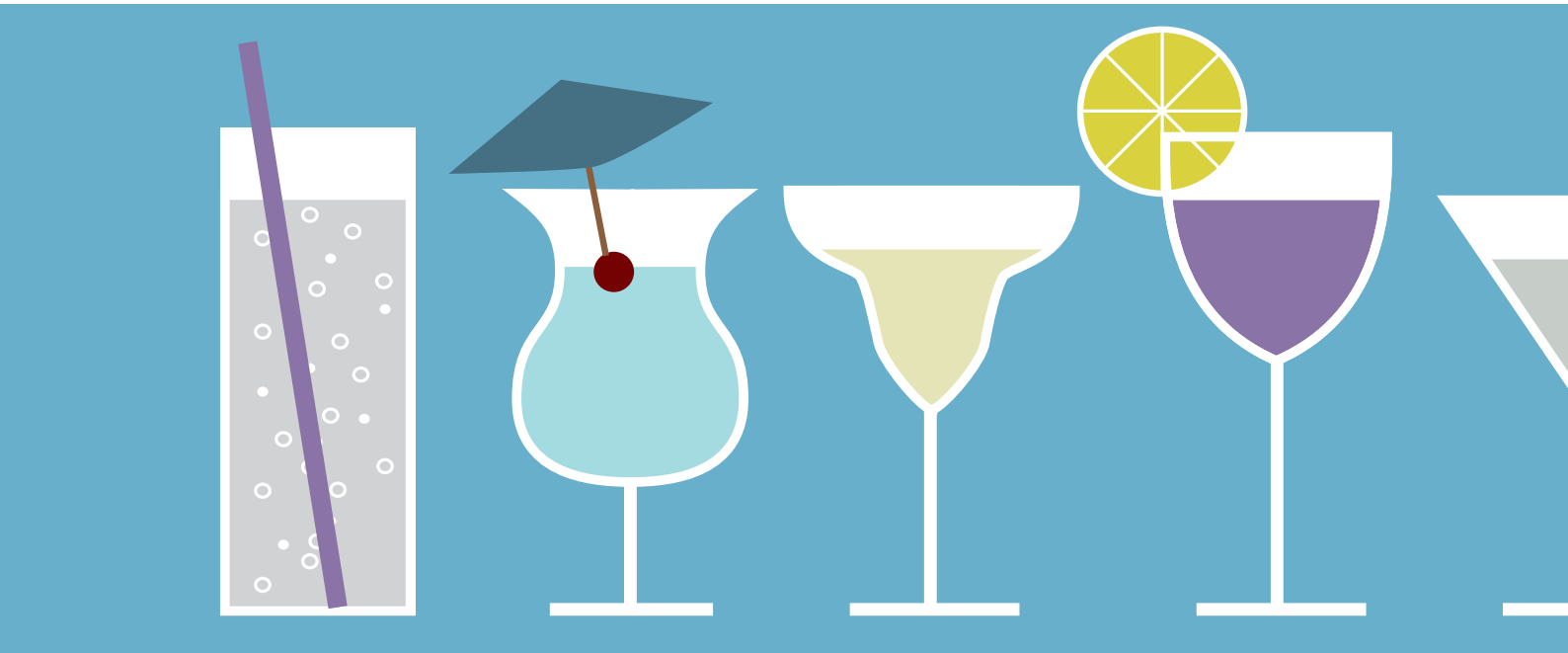
Several UK and US studies indicate that HIV-positive people are more likely to drink heavily, and to be classified as having an alcohol problem. Looked at from the other direction, people with problematic alcohol use (such as clients of rehabilitation programmes) are more likely to have HIV. Rates of alcohol use are high amongst several groups at particular risk of HIV, including young people, injecting drug users, gay men and African immigrants.

It is hard to verify whether gay men tend to drink more or less than heterosexual men as most large surveys have not asked about sexual orientation, but one UK survey found that 85% of gay men drank alcohol during the past year and 11% were concerned about their drinking.[4] A 2001 survey of gay and bisexual men in four large US cities produced strikingly similar results: 85% used alcohol and 8% reported heavy or frequent use.[5]

A recent survey, spearheaded by the Black Health Agency, of 40, mostly heterosexual, HIV-positive African men and women living in the north of England found that about one-third drank alcohol more than four times a day, with some men consuming 10 to 15 cans of beer in an evening.[6] Depression, a desire to forget about issues like being HIV-positive or lack of legal immigration status, financial issues and loneliness were cited as key reasons why people drank.

Alcohol and HIV transmission

Alcohol use can lead to a higher risk of HIV transmission. Research looking at both gay men and heterosexual men and women has shown that people who drink more tend to have more sexual partners, on average, and are less likely to use condoms. That doesn't mean that alcohol causes you to have sex. It may make you less careful as well as less choosy, though. This may particularly apply to women and, in some circumstances, gay men; alcohol-impaired sexual performance may be less of an issue (and more of a cause of vulnerability, because while many think



drunk men are best avoided, men may regard drunk women as targets).

How much you drink at one sitting appears to be a bigger risk factor than frequency of drinking. One US study found that HIV-negative gay and bisexual men who reported heavy alcohol use during the past six months or binge drinking right before or during sex were more likely to engage in unprotected anal intercourse with an HIV-positive partner or with a partner whose HIV status was unknown to them.[7]

Another US study found that women who reported binge drinking were twice as likely as other women to have multiple sexual partners, three times more likely to report having anal sex and five times more likely to be diagnosed with gonorrhoea.[8]

Alcohol is linked to risky sexual behaviour worldwide.[9] What's more, drinking and sex – especially commercial sex – often take place in the same venues. Alcohol increases the likelihood of sexual violence and non-consensual sex and, for women, drinking can increase vulnerability to sexual victimisation.

The Black Health Agency survey suggested that drinking is associated with risky sexual behaviour amongst HIV-positive Africans, a particular concern since more than half had not disclosed their status to their regular partner.

"Alcohol and passion may not present the most favourable ground for clear thinking, better condom use and sexual equality in power decisions regarding sex," understates Gertrude Anyango-Wafula, the BHA's co-ordinator for HIV and sexual health services.

According to Sigma Research[4], most gay men said they drink alcohol to relax, to be more sociable, to boost their confidence, and to escape temporarily stress and worries. Others said drinking helped them overcome their inhibitions and made them more sexually adventurous. HIV-positive men also said alcohol helped them deal with feelings of isolation and concerns about disclosing their status.

People may simply forget to practise safer sex when drinking, but more complex psychological processes are probably involved. People who are under the influence may give more weight to their immediate desires and feelings and less to negative future consequences – so-called 'alcohol myopia'.[10] An alternative explanation is that some people have what have been called 'type T' (for thrill-seeking) personalities that predispose them to seek sensation and take chances, which can include both risky substance use and risky sex.

Seth Kalichman, from the University of Connecticut, and his co-workers found that sensation-seeking predicts HIV risk behaviour and alcohol use in studies conducted amongst both gay men in the US[11] and heterosexual men and women in South Africa.[12] "Men are more likely to drink and engage in higher risk behaviour whereas women's risks are often associated with their male sex partners' drinking," they concluded.

Health consequences

Alcohol affects every organ and system in the body from the brain, to the digestive system, to the skin and bones.

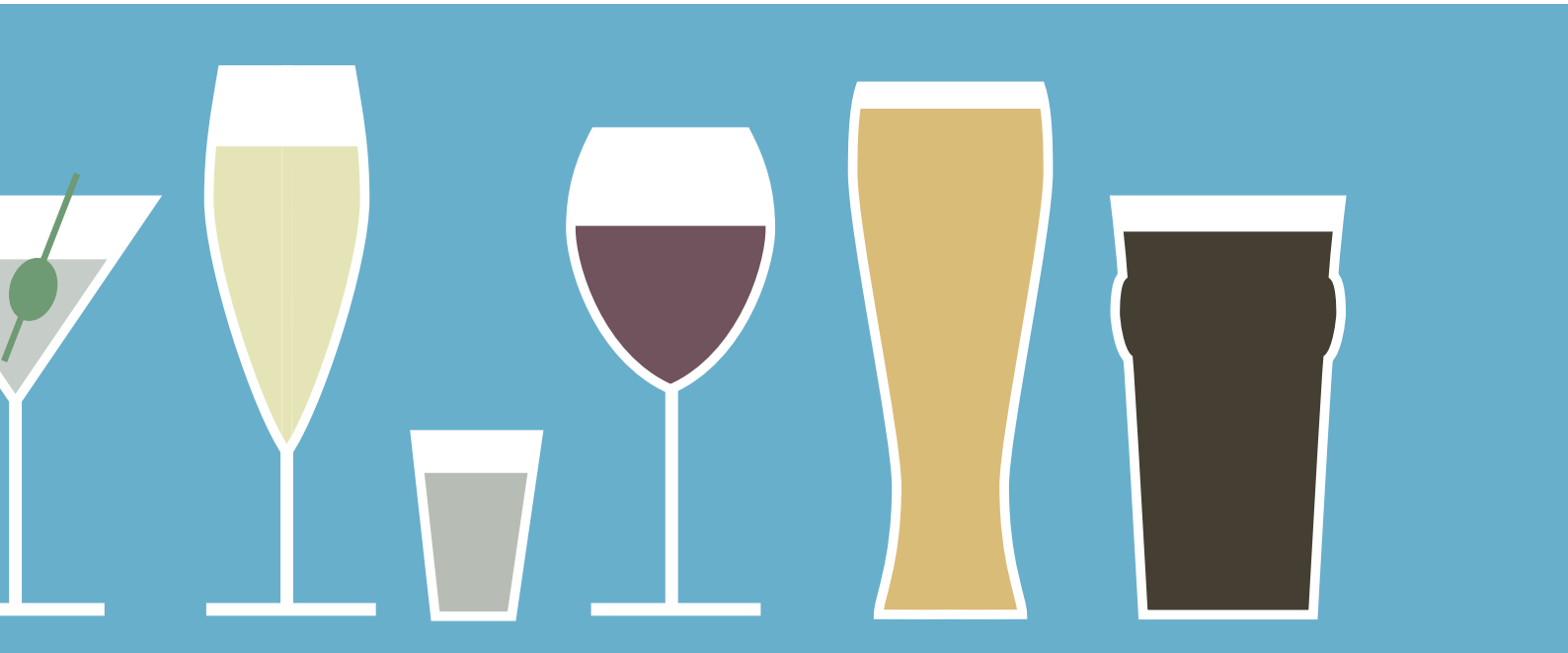
Effects on the liver

The liver, which filters and processes toxic chemicals in the body, is the organ most heavily affected by alcohol. In the majority of people the liver is a remarkably resilient organ that deals with an awful lot of alcohol during a human lifetime. However, approximately one-third of heavy alcohol users develop alcoholic hepatitis after about ten years on average, and about 15% go on to develop cirrhosis (a build-up of scar tissue that severely impairs liver function).[13,14] A recent study in Southampton found that most patients hospitalised with cirrhosis drank on a daily basis, often starting at a young age.[15] People with hepatitis B or C develop alcohol-related liver disease sooner.

Chronic hepatitis B or C, and especially HIV and hepatitis co-infection, can cause the same outcomes, and alcohol is especially harmful for people with viral hepatitis. An estimated 10% of people with HIV in the UK are co-infected with hepatitis B or C, which are associated with faster liver disease progression.

Not only does alcohol accelerate liver damage, it also reduces response to interferon treatment for hepatitis C.[16]

The good news is that the liver is a resilient organ that can repair itself. While the damage due to late-stage cirrhosis is likely to be permanent,



stopping or cutting back on drinking before this point can allow the liver to recover.

Effects on the brain

There is a widespread belief that alcohol kills brain cells, but alcohol's specific effects on the brain are actually caused by altering how nerve cells communicate. Brain function typically returns to normal after a bout of drinking, but chronic heavy alcohol use can lead to permanent memory loss due to deficiency of vitamin B_1 (thiamin), absorption of which is impaired by alcohol. Even moderate drinking may impair short-term memory and heavier alcohol use can cause longer periods of memory loss (blackouts).

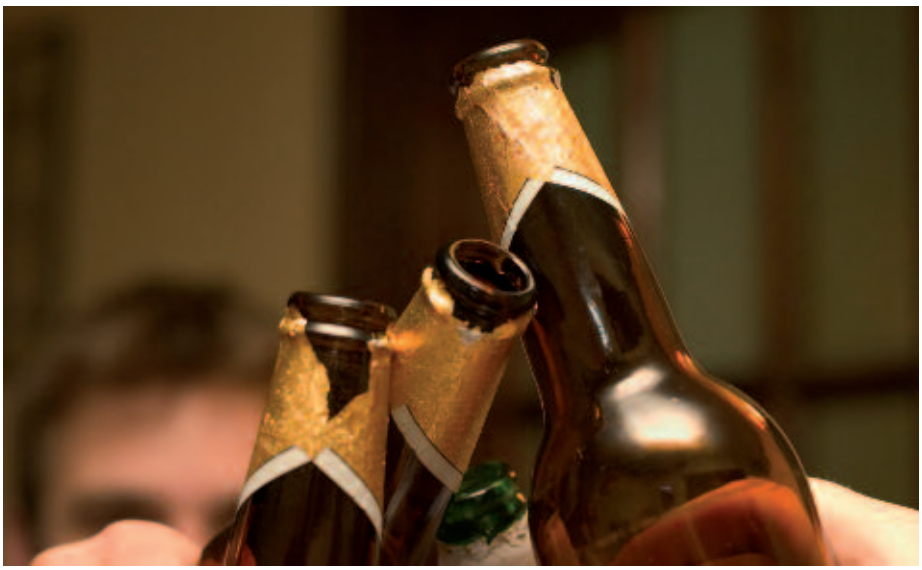
Some studies suggest that alcohol increases the risk of neurocognitive impairment in people with HIV, though the effects of alcohol are less apparent in people on antiretroviral treatment.

One study looking at memory deficits found that HIV-negative alcoholics and HIV-positive people who did not abuse alcohol generally performed at normal levels, but HIV-positive alcoholics showed an impaired memory for events.[17] Another found that HIV-positive people with a history of alcohol abuse continued to have significantly worse verbal scores and reaction times, suggesting that heavy drinking may have silent residual effects predisposing people to HIV-related cognitive impairment.[18]

Other effects

Alcohol can also affect the digestive system, increasing the risk of stomach problems (including cancer), ulcers and pancreatitis (inflammation of the pancreas). Alcohol is linked to metabolic problems, already a concern for people with HIV. Chronic heavy drinkers may be overweight yet malnourished because alcohol contains empty calories and suppresses appetite. Alcohol can alter blood sugar levels, whilst pancreas damage may decrease insulin production. Heavy drinkers are more likely to develop cardiovascular disease and certain types of cancer, and are more like to die early from all causes combined.

A study of nearly 300 HIV-positive people with a history of alcohol problems found that moderate and heavy drinkers were about twice as likely as current abstainers to report having lipodystrophy (changes in body fat distribution), though the difference did not reach statistical significance.[19]



Researchers in the USA looked at drinking and heart disease in nearly 5000 men in the Veterans Aging Cohort Study.[20] Amongst HIV-positive – but not HIV-negative – men, 'hazardous' drinking (more than 14 drinks per week) and 'binge' drinking (six or more drinks at a time) were associated with a higher risk of cardiovascular disease compared with infrequent or moderate drinking, even after adjusting for traditional risk factors.

You may also have read that moderate drinking (one or two units a day) can have beneficial effects. Some studies suggest that alcohol can protect against heart disease, but this research has not looked at people with HIV. Eating healthily and exercising also reduce the risk of heart disease.

Alcohol and HIV

Light or moderate drinking does not appear to be harmful for most people with HIV unless they have other medical conditions such as hepatitis. But there is some evidence that heavy use may contribute to HIV disease progression.

Alcohol suppresses the activity of some defensive immune cells, which may explain why chronic heavy drinkers get more infections such as pneumonia. At the same time, alcohol promotes overall immune activation and inflammation – factors suspected of playing a role in non-AIDS-defining conditions such as cardiovascular disease amongst people with HIV.

Alcohol may make cells more susceptible to HIV infection, and increased immune activation and higher inflammatory cytokine (chemical messenger) levels can trigger HIV replication. But it is not clear whether alcohol directly raises viral load, lowers CD4 cell counts or speeds up HIV disease progression, since laboratory and animal studies have produced mixed findings.

Two studies involving monkeys found that the monkeys given alcohol developed viral loads that were 64 to 85 times higher in early infection in the blood and, in the first study, in the brain.[21,22] A later follow-up found that monkeys given alcohol at levels equivalent to binge-drinking progressed to AIDS more rapidly, in an average time of 374 days compared with 900 days for the non-alcohol group.[23]

Turning to humans, most studies that have reported less robust viral load suppression or CD4 cell recovery amongst alcohol users have not adequately controlled for adherence, illegal drug use or other confounding factors.

There are some studies which have, though. Researchers looking at 1433 HIV-positive people seen at an urban clinic found that heavy alcohol use was associated with less viral load suppression after accounting for illegal drug use and poorer adherence.[24]

Similarly, amongst 1691 participants in the US Women's Interagency HIV Study, both heavy alcohol use and crack

cocaine independently predicted disease progression while on treatment, even after taking adherence differences into account.[25]

A team in Boston found that amongst 595 HIV-positive people from two cohorts followed for up to seven years, heavy alcohol use was associated with a lower CD4 cell count *only* amongst untreated individuals – and there were no notable differences in CD4 count or viral load amongst people on antiretroviral therapy. This study suggests that adherence is not the only reason alcohol has an effect on disease progression. Untreated heavy drinkers had an average CD4 count of about 50 cells/mm^3 less than teetotallers. CD4 cell percentages were similar, suggesting that alcohol had an effect not only on CD4 T-cells but on lymphocytes overall.

A recent study of more than 200 participants in Miami, HIV-positive people who drank two or more 'standard drinks' per day (that's just one-and-a-quarter pints of UK pub-strength lager) were nearly three times more likely to see their CD4 cell count fall below 200 cells/mm^3 than teetotalers, and drinkers not on ARVs had more than a sevenfold risk.[26] The researchers concluded that alcohol may have a direct effect on CD4 count, while its effect on viral load was due to reduced adherence.

These findings imply that heavy drinkers might need to start antiretroviral therapy sooner after infection because they lose CD4 cells faster. But the researchers emphasised that the effect of alcohol was modest and was not apparent for people on treatment, perhaps because the large benefit of therapy overshadows the smaller detrimental effect of alcohol.

Alcohol, HIV treatment and adherence

Research shows that people with alcohol problems are less likely to get tested for HIV and slower to seek care after testing positive, but it is difficult to tease out the influence of alcohol versus co-existing factors like illegal drug use, poverty and mental illness.

Alcohol has not been shown to interact in any major way with antiretroviral medications. But heavy drinking – and liver damage caused by chronic heavy use – can potentially interfere with enzymes in the liver that process certain drugs, including protease inhibitors. Heavy drinkers and people with liver damage are also more susceptible to drug-related liver toxicity.

Alcohol can react badly with some medications used to treat opportunistic infections (for example, rifampicin and metronidazole). It also can interact dangerously with drugs for non-HIV-related conditions; using alcohol with sedatives or illegal narcotics can cause slowed breathing and heart rate and even cause coma or death. Paracetamol (acetaminophen) can cause liver damage when combined with even a small amount of alcohol, as can the TB drug isoniazid. Consult your clinic or a pharmacist about whether it is safe to drink whenever you are prescribed new drugs.

HIV treatment can only work if it is taken properly. If a bout of drinking leads to vomiting, it may be necessary to repeat a dose (generally if vomiting occurs within an hour of taking it).

Considerable research shows that alcohol use, especially binge drinking, increases the likelihood of poor adherence to HIV treatment. One study found that binge drinkers and heavy drinkers more often reported poor adherence due to forgetting or running out of medications.[27] A meta-analysis of 40 studies looking at the link between alcohol and adherence found that people who drank alcohol were approximately 50% – and heavy drinkers 60% – less likely to be classified as adherent.[28]

"Drinking quantity, more than frequency of drinking, is associated with non-adherence," said lead author, Christian Hendershot.

This supports prior research showing that alcohol seems to have more effect on adherence in women. A 2007 study, for example, found that alcohol use predicted decreased adherence amongst women, but not men.[29]

HIV psychology researcher Seth Kalichman has uncovered another reason for reduced adherence.[30]

"It is common for people to believe that they should not mix their medications with alcohol," he told *HTU*. "We have found that some people will stop taking their medications if they are drinking because they believe they should not mix them."

Kalichman and others[31,32] have shown that tailored alcohol interventions for people with HIV can be effective, both in industrialised countries and in Africa. Successful programmes not only help people reduce problem drinking, but also decrease high-risk sex and drug use behaviours and improve treatment adherence and response.

The good news is that most research has not shown that moderate drinking worsens HIV disease progression or interferes with treatment response. But studies focused on heavy drinking amongst socially marginalised groups have not really looked at the effects of typical social drinking within the larger HIV-positive population: problem drinking is often lumped in with other kinds of substance use, whilst moderate drinking receives little attention. Sigma's *Wasted Opportunities* report[4] found that most gay men with problem alcohol use did not consider themselves alcoholics and only a minority sought help from social or health services. Healthcare providers may need to be more proactive in asking patients about how drinking affects their lives.

Alcohol use is an important consideration for people with HIV and warrants more awareness in both research and clinical practice. ■

getting help

There is plenty of help available if you think you have an alcohol problem – or simply want to cut back on the amount you drink.

Talk to the healthcare team at your clinic. There are some services specifically for gay men and other people affected by HIV. Support groups such as Alcoholics Anonymous are available in most areas.

More information on alcohol, and on cutting down, is available from NHS Choices at www.drinking.nhs.uk or from Drinkline on 0800 9178282. Other useful contacts can be found at www.drinking.nhs.uk/more-information/useful-contacts/.

staying hepat

It's still not clear exactly how HIV-positive gay men are contracting hepatitis C through sex. Until we know with certainty, *Derek Thaczuk* asks, can we avoid co-infection?

Questions about sexual transmission of the hepatitis C virus (HCV) have been controversial since day one. Despite earlier uncertainty, there is no longer any question that HIV-positive men are acquiring HCV through sex with other men (as are HIV-negative gay men, although much less frequently). How best to protect ourselves depends on which specific sexual activities are riskiest – an issue for which the evidence is suggestive but not yet conclusive.

In the great majority of cases, the hepatitis C virus is transmitted by direct blood-to-blood contact: through needlestick injuries, by sharing needles or other injecting drug equipment. It can also be passed from mother to child during childbirth. (Before screening of donated blood became routine in 1990, many people also became infected through blood transfusions and infected blood products.)

At first it was believed that only blood-to-blood contact could transmit HCV. Early research in heterosexual couples found that sexual transmission was very rare: many studies found *no* occurrences in the couples followed, even over periods of many years.[1]

However, the reality has proven quite different in HIV-positive gay and bisexual men. Despite some initial scepticism, sexual transmission is now the well-established cause of outbreaks of acute HCV infection among gay and bisexual men in a growing list of countries.

The first reports came from the UK in 2002, when physicians at two of London's largest HIV clinics reported new hepatitis C infections among HIV-positive gay men who did not use needles or have any other known risk factors for HCV, apart from having unprotected sex. The number of known UK cases has continued to grow, and outbreaks have also been documented in the Netherlands[2], Switzerland[3], France[4], Germany, Australia[5] and the US.[6] (Hepatitis C also has an international passport: detailed genetic analyses have shown that it is being transmitted from country to country among HIV-positive men.[7])

Rates are on the rise

Overall rates of hepatitis C infection (by any means of transmission, sexual or otherwise) are on the rise among HIV-positive gay and bisexual men in London and Brighton. According to data from HIV and sexual health clinics in those two cities, a total of 389 HIV-positive gay or bisexual men were diagnosed with hepatitis C between 2002 and 2006 (352 in London and 37 in Brighton).[8] Infection rates increased by 20% each year during that time, from 56 cases in 2002 to 91 in 2006 – a trend that appears to be continuing.[9]

Over the same time interval, only six cases of HCV were reported among HIV-negative men (or those who did not know their status). Outbreaks in every country, in fact, are almost exclusively confined to HIV-positive men. This finding is not yet fully understood, and we will return to it later on.

free of titis C

What kinds of sex are risky?

Fisting has often been identified as the single largest risk factor for sexual HCV transmission. One of the largest UK studies compared 60 recently HCV-infected, HIV-positive gay men to 130 HIV-positive 'controls' who did not have hepatitis C. Men in this study who were insertive in fisting (fisting 'tops') were about three times more likely to have contracted HCV, and receptive partners (fisting 'bottoms') four times more.[10] In another study of over 300 men, fisting appeared riskier still, carrying a nine-times greater risk of HCV infection, though this figure was only based on eleven actual cases of recent HCV infection.[11]

However, men who have never fisted or engaged in other 'heavy' anal play have also become infected. Also, at least one study of HIV-positive gay men in New York did not find fisting to be significantly riskier than unprotected intercourse alone (a difference that may reflect different patterns of infection and sexual behaviour in different locations).[12] Fisting may account for significant numbers of hepatitis C infections, but it is probably not the only way the virus can be spread sexually.

Studies have consistently found other behaviours that increase the risk of contracting HCV sexually, including the use of sex toys (dildos), group sex, having large numbers of sexual partners, using recreational drugs during sex, rimming and having sexually transmitted infections (STIs) such as syphilis and herpes.[13,14,15] Yet the single most common factor reported by men who have become HCV-infected is unprotected anal sex.

Many experts now believe that increasing numbers of men are becoming infected through barebacking (unprotected anal sex) alone. "I think the primary route of HCV transmission has shifted," says Martin Fisher, consultant physician at Brighton & Sussex Hospitals NHS Trust. "With the first cases we saw, the majority of those people reported more than just unprotected anal intercourse. They tended to be people with multiple partners and fairly vigorous sexual activity such as fisting and toys, often taking recreational drugs as well. The majority of individuals I now see with acute, newly diagnosed HCV don't report those risk factors, except for unprotected sex."

In the US, where sexually transmitted HCV only surfaced among gay men more recently, barebacking appears to be a greater contributor than fisting. Daniel Fierer, Assistant Professor of Medicine at New York's Mount Sinai School of Medicine, was one of the investigators on the New York study mentioned above. Fierer and team "looked at a relatively small number of patients, but we did a very carefully matched statistical analysis. When we removed people with any history of injection drug use, we found that fisting and sex while high were not significant risks: it was largely receptive unprotected sex. Insertive partners were not the ones becoming infected."

Blood or semen?

Identifying risky activities is not the same as explaining just how HCV transmission occurs – a question that is not yet definitively answered. As Daniel Fierer puts it, "Men who are getting infected are engaging in a lot of activities. That tells us the milieu in which it's happening, but doesn't necessarily disentangle the causal factors."

The link between fisting and HCV transmission suggests that the virus is most easily transmitted through

damaged rectal tissues – an explanation that seems plausible and perhaps intuitively 'right'. Delicate, blood vessel-laden rectal tissues are easily damaged by fisting or other intense anal play (such as large dildos and sex toys), creating an open pathway for infection. Rectal tissue could conceivably be vulnerable to infection even if not 'roughed up' by heavy play.

But virus from the infected partner still has to find its way there – and how it does so is still being debated. Is it through blood, semen, or both? Whether HCV can be transmitted through semen is under debate. Studies have found the virus at detectable, but low, levels in the semen of 10 to 40% of HCV-infected men.[16] Fisher and Fierer both point out that HCV has been found in semen at higher levels in HIV-positive than in HIV-negative individuals. Yet even in HIV-positive men, seminal HCV levels are usually so low that many experts doubt they could cause infection. A small, recent study detected HCV in the semen of only a minority of co-infected men in the UK, and levels in semen were at most a few hundredths of a percent of those usually found in the bloodstream. Seminal HCV levels in the study were 230 IUs (international units)/ml or less. An international unit can vary from 0.9 to 5.2 copies/ml, depending on the test used, so this translates into 200 to 1200 copies: but most detectable seminal viral loads in this study translated into below 150 copies/ml by any test. In contrast, typical bloodstream levels run into the millions of copies/ml.[17]

Risks on top of risks

It could be argued that risky sex, whether barebacking or fisting, are contributing factors: i.e., the more risky activities you engage in, the more likely you are to contract HCV. One analysis of a group of men in the UK found just such a 'cumulative' outcome when four separate factors were considered – unprotected anal sex, group sex, recreational drug use, and 'mucosally traumatic' practices like fisting and sex toys. Two or more of these activities made for a nine times greater risk of infection, but engaging in three or all four increased the risk by more than 23-fold.[18]

With the first cases we saw, the majority of those people reported multiple partners and fairly vigorous sexual activity such as fisting and toys, often taking recreational drugs as well.

The majority of individuals I now see with acute, newly diagnosed HCV don't report those risk factors, except for unprotected sex.

Martin Fisher
Brighton and Sussex Hospitals NHS Trust

Group sex sessions may provide even more opportunity for the virus to be spread. In a study from Germany, although unprotected anal sex was widespread among the men studied, only being fisted (receptive), rectal bleeding, and drug use during group sex were significant risks for sexual HCV transmission. The researchers went on to conjecture that in group sex situations, some people may serve as 'carriers' who pass HCV between others.[19] Specifically, fisting 'tops' (insertive partners) with multiple 'bottom' (receptive) fisting partners in the same session may carry HCV-infected blood from one to the other.

Not everyone buys into this hypothesis – Fierer finds it "a tortured explanation" – yet even without it, group sessions still bring together a wide range of risks. They often exclusively involve unprotected sex between HIV-positive men who have chosen to serosort (i.e., restrict unprotected sex to other HIV-positive partners) and often involve heavy sex play and recreational drugs. Together, these factors could conspire to produce a setting ripe for HCV transmission.

The role of HIV

With new HCV infections amongst HIV-positive men vastly outnumbering those in HIV-negative men, HIV itself clearly plays a central role in HCV transmission. Precisely what that role is has yet to be determined. Behaviour, rather than biology, may be at least part of the explanation: "if you've recently acquired HIV then you're likely to be in a high-risk period of your life, which could put you at risk of HCV as well," says Fisher.

In fact, many HIV-positive gay men who contract hepatitis C sexually seem to do so shortly after their HIV infection. A study conducted at St Mary's Hospital in London found that 7% of gay men diagnosed with HIV at the hospital

between 1999 and 2006 went on to become infected with HCV through sex. On average, the time between HIV infection and diagnosis of hepatitis C was just under two years.[20]

Still, any difference in sexual behaviour between HIV-positive and HIV-negative men does not seem sufficient to explain the enormous difference in rates of HCV. Martin Fisher suggests that, "We'd see more crossover from HIV-positive to HIV-negative men if that were the only factor. So I think there is something immunological going on as well, that we haven't yet characterised, that puts you at greater risk of acquiring HCV if you are HIV-positive."

Sex & drugs

Using recreational drugs as a sex stimulant ('sex while high') is also repeatedly identified in studies as another risk factor for hepatitis C transmission. This may be due to the way drug use influences sex (men who get fisted may be more likely to use drugs), and/or by the way the drugs themselves are taken – and gay men who use drugs may not be aware of all the risks.

For instance, HCV is known to be easily spread through shared straws or other equipment for snorting drugs: as a straw or 'bullet' gets passed around, miniscule amounts of blood can pass from one person's nasal membranes to the next. Needle use, with all its potential risks for HCV transmission, is also not unknown among gay men. HCV can easily be spread through shared equipment other than needles themselves. Spoons or other equipment used to dissolve drugs for injection, and filters used to filter substances, can easily transfer HCV from a used needle to a new one.

What's a poz gay man to do?

Of course, many HIV-positive gay men use condoms as a matter of course and do not fist or go to sex parties: they are likely to be as safe from contracting HCV as it is possible for a sexually active gay man to be. At the other end of the spectrum, fisting, group sex and drug use appear to present the greatest risks. But what about those HIV-positive gay men who choose to serosort but do not engage in more hardcore activities like fisting and group sex? These men may face the biggest uncertainties about HCV risk – in the face of which, the most frequent advice is caution.

As Martin Fisher puts it, "We would like to be able to say, 'HCV is transmitted like this, and therefore here is what you need to do to avoid getting it.' Unfortunately I think we're at too early a stage to be able to give such definitive guidance, and I think we have to be honest about that. We simply have to tell people what we know: that there probably is an increased risk with any sexual activity with exposure to semen, and almost certainly more so with blood."

According to Daniel Fierer, the bottom line is "awareness in the gay community that you *can* get HCV sexually. This is a new and unfortunate risk in serosorting. Let's assume the risk is significant, and take precautions. That may not be popular, but it is simple."

One challenge is that men who have chosen to serosort may already have disengaged from standard safer-sex messaging. (Dire, but overblown, warnings of reinfection with HIV 'superbugs' may well have bolstered scepticism toward "condoms for all, all the time" messages.)

That, says Marc Thompson of the Terrence Higgins Trust (THT), was a significant challenge for his organisation in providing information to positive men who bareback. "We knew we were dealing with men who were already quite well-informed about safer sex issues, who didn't engage with typical safer-sex messaging, and who had made decisions around their own sexual health already."

Their first step, then, was not to talk but to listen. In a series of focus groups, and others at THT met with the men likely most at risk for HCV, those who frequently fist, have rough sex, and use drugs. Those who had already been co-infected with HIV and HCV had a clear message for their peers: hepatitis C is not just another STI. "Gay men may think of sexually transmitted infections (STIs) as things that can often be treated fairly easily: a trip to the clinic, a couple of pills. The men in our groups wanted us to stress how debilitating hepatitis C is, and how completely different HCV treatment is from the treatments for other STIs." That message – that HCV treatment is lengthy and hard to tolerate – was "loud and clear," says Thompson.

Which brings us back to the question: in the absence of certainty about what's risky, what is the best prevention advice? "We're just trying to present all the info as it stands," says Thompson. "We're not the condom police, but we have not ruled out unprotected anal intercourse as a means of HCV transmission, so that has to be put out there, along with all the other information we have to date."

Finally, one more factor is probably contributing to hepatitis C transmission as well as worsening life for those infected: the fear, shame and stigma of the disease. Gay men with hepatitis C have said they feel "grubby, skanky, isolated and ashamed." They have called HCV "the big new white elephant in the room", something gay men are "scared of, but that nobody is talking about." Men with HCV have described an "us and them situation" in which their dual diagnosis excludes them from the "camaraderie of just being HIV-positive."[21]

Clearly, as a community we have a mandate to help HIV-positive men avoid co-infection. Yet, as we continue to battle stigma against people with HIV, it would be a sad irony if our own community opened its arms to people with one virus but turned its back on those with another. ■

news in brief

HIV testing

Slow progress towards routine tests

Only a minority of patients in hospital and GP settings are receiving HIV tests where they are indicated, according to surveys presented at the British HIV Association (BHIVA)/British Association for Sexual Health and HIV (BASHH) spring conference in Manchester.

It is now a year and a half since national guidelines were issued recommending that HIV tests should be offered to all adults presenting for care who live in areas where more than 0.1% of the population has HIV or who present with symptoms suggesting HIV infection.

The proportion of eligible patients who were offered tests in the surveys ranged from 14 to 40%. When patients were offered tests, acceptance rates were high.

A survey from Brighton[1] of patients admitted to hospital in late 2009 found that 40% were tested for HIV. There were two new HIV diagnoses, but an anonymous survey of HIV prevalence in the same patients found that nine other patients had HIV and had left hospital undiagnosed.

"Although testing is recommended as routine, clinicians still seem to be targeting patients, yet failing to identify the majority of undiagnosed," commented presenter Nicky Perry.

A survey from Basildon Hospital in Essex of 347 patients with symptoms suggestive of HIV found a low rate of HIV testing (14%) in the year after the guidelines were issued.[2]

One reason for the low testing rates was because HIV results were not available on the hospital's computerised test results database.

But, the presenter commented: "Some of the reasons are evidence of an old-fashioned view of those at risk of HIV. [One clinician said] 'I only test if the patient is really camp'." After these data were presented at the hospital, HIV test results were put on the database and the rate of HIV tests increased by 60%.

A large survey looked at all 41,095 HIV tests performed in 2008 by the laboratory at Guy's and St Thomas's Hospital, which covers the highest HIV prevalence area in the UK.[3] The majority came from STI and antenatal clinics, but 14% came from GPs. The diagnosis rate in these tests was actually higher than in STI patients (1.12%).

Sexual health

Sharp increase in LGV cases

Cases of lymphogranuloma venereum (LGV) have tripled in the first quarter of 2010, compared to the same period in 2009, Cassandra Powers of the Health Protection Agency told the BHIVA/BASHH conference.[1]

LGV is a previously rare sexually transmitted infection, caused by specific strains of *Chlamydia*. If left untreated, symptoms can be complex and severe, including inflammation of the anus or rectum. Cases were first noticed in 2004 but by 2008 there was hope that this new epidemic was levelling off. Almost all cases of LGV are in gay or bisexual men, and three-quarters of those infected are HIV-positive.

The monthly number of cases increased each month from September 2009 onwards. In the first quarter of 2010, there were 113 cases, a 209% (threefold) increase from the first quarter of 2009. Cases continue to be concentrated in London, Manchester and Brighton, but not exclusively.

Supplements

Zinc helps CD4 counts

A placebo-controlled trial[1] of zinc supplementation in 231 HIV patients, 62% of them taking HIV treatment, found that patients taking zinc were only 24% as likely to experience their CD4 cell count falling below 200 cells/mm^3 as patients taking a placebo. Zinc supplementation also significantly reduced the frequency of diarrhoea.

In this study patients either took a daily dose of zinc (15mg men, 12mg women) or a placebo. The study lasted 18 months, and the patients were monitored at regular intervals.

The only four patients with initially undetectable viral loads whose CD4 counts fell below 200 were all taking placebo rather than zinc. However, only 42 patients in this study (18%) had undetectable viral loads, and this could have been due to chance.

There was no evidence that zinc supplements lowered viral load, so this was not the reason people taking zinc were less likely to develop low CD4 counts. There was also no evidence that taking zinc supplements reduced the risk of death: eleven patients in the treatment arm died compared to eight in the placebo arm, but the difference was not statistically significant.

On entry to the study, a third of patients reported a history of diarrhoea within the last twelve months, and 12% said that this had been severe. Zinc supplementation reduced the risk of diarrhoea by 60% and the investigators found a significant link between low zinc levels and diarrhoea.

The investigators hypothesise that zinc supplementation helps patients' thymus glands produce more T-cells. They

conclude: "This evidence supports the recommendation of zinc therapy as a safe, simple, and cost-effective tool to improve the immune response."

Hepatitis C

Hepatitis C in semen unlikely to explain transmission

Hepatitis C virus (HCV) is only detectable in the semen of a minority of co-infected HIV-positive men, and even then at very low levels, a small study presented at the BHIVA/BASHH conference has found.[1]

This study adds to the weight of evidence that transmission of HCV during sex is via blood, not via semen, and leaves researchers looking for an explanation as to why HIV-positive men are approximately 50 times more likely to acquire HCV than HIV-negative men.

The study recruited ten men from the HCV cohort at the Mortimer Market Centre in London who had been diagnosed less than six months ago and ten who were chronically infected.

Detectable viral load in fact turned out to be non-significantly more common in the chronic controls. Two out of ten had a detectable viral load at baseline (37 and 230 international units per millilitre – IUs/ml). None of the acutely infected men did, though one developed a detectable, but very low, viral load (14 IUs/ml) at one month.

At six months two acutely infected men had had a detectable viral load at some point in the study compared with four chronically infected men, but all very low, with no measurement over 230 IUs/ml compared with figures in the millions for blood viral load. In addition, no correlation was seen in this study between seminal and blood viral loads.

references to all articles (continues on page 15)

START... and why the time is now [page three]

1 See http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf

2 See http://i-base.info/home/community-statement-supporting-start-trial

to your health! [page four]

1 World Health Organization – Global Health Observatory data. See http://apps.who.int/ghodata/

2 ONS *Drinking: adults' behaviour and knowledge in 2009.* Opinions Survey Report No. 42. 2010.

3 Bellis M et al. *Cross-sectional measures and modelled estimates of blood alcohol levels in UK nightlife and their relationships with drinking behaviours and observed signs of inebriation.* Substance Abuse Treatment, Prevention and Policy 5(1):5, 2010.

4 Keogh P et al. *Wasted opportunities: problematic alcohol and drug use among gay men and bisexual men.* Sigma Research, 2009. See www.sigmaresearch.org.uk

5 Stall R et al. *Alcohol use, drug use and alcohol-related problems among men who have sex with men: the Urban Health Study.* Addiction 96(11):1589-1601, 2001.

6 Wafula GA et al. *Survey report on treatment and nutrition information needs of people living with HIV carried out in the Northwest and North East of England.* Unpublished study, Black Health Agency.

7 Colfax G et al. *Substance use and sexual risk: a participant- and episode-level analysis among a cohort of men who have sex with men.* Am J Epidemiol 159(10):1002-1012, 2004.

8 Hutton H et al. *The relationship between recent alcohol use and sexual behaviors: gender differences among sexually transmitted disease clinic patients.* Alcohol Clin Exp Res 32(11):2008-2015, 2008.

9 World Health Organization (author Bianchi G) *Alcohol use and sexual risk behaviour: a cross-cultural study in eight countries.* 2005.

10 David K et al. *Alcohol's effects on sexual decision making: an integration of alcohol myopia and individual differences.* J Stud Alcohol Drugs 68(6):843-851, 2007.

11 Kalichman S et al. *Sensation seeking as an explanation for the association between substance use and HIV-related risky sexual behavior.* Arch Sex Behav 25(2):141-154, 1996.

12 Kalichman S et al. *Sensation seeking and alcohol use predict HIV transmission risks: prospective study of sexually transmitted infection clinic patients, Cape Town, South Africa.* Addict Behav 33(12):1630-1633, 2008a.

13 Mann R et al. *The epidemiology of alcoholic liver disease.* Alcohol Res Health 27(3):209-219, 2003.

14 Maher J. *Exploring alcohol's effects on liver function.* Alcohol Health Res World 21(1):5-12, 1997.

15 Hatton J et al. *Drinking patterns, dependency and life-time drinking history in alcohol-related liver disease.* Addiction 10 Feb. 2009.

16 Mallat A et al. *Environmental factors as disease accelerators during chronic hepatitis C.* J Hepatology 48(4):657-665, 2008.

17 Fama R et al. *Working and episodic memory in HIV infection, alcoholism, and their comorbidity: baseline and 1-year follow-up examinations.* Alcoholism: Clinical & Experimental Research 33(10):1815-24, 2009.

18 Green J et al. *The effect of previous alcohol abuse on cognitive function in HIV infection.* Am J Psychiatry 161(2):249-254, 2004.

19 Cheng D et al. *Alcohol consumption and lipodystrophy in HIV-infected adults with alcohol problems.* Alcohol 43(1):65-71, 2009.

20 Freiberg MS *The association between alcohol consumption and prevalent cardiovascular diseases among HIV-infected and HIV-uninfected men.* J Acquir Immune Defic Syndr 53(2):247-53, 2010.

21 Kumar R et al. *Increased viral replication in simian immunodeficiency virus/simian HIV-infected macaques with self-administering model of chronic alcohol consumption.* J Acquir Immune Defic Syndr 39: 386-390, 2005.

22 Bagby G et al. *The effect of chronic binge ethanol consumption on the primary stage of SIV infection in rhesus macaques.* Alcohol Clin Exp Res 27:495-502, 2003.

23 Bagby G et al. *Chronic binge ethanol consumption accelerates progression of simian immunodeficiency virus disease.* Alcohol Clin Exp Res 30 (10): 1-10, 2006.

24 Chander G et al. *Hazardous alcohol use: a risk factor for nonadherence and lack of suppression in HIV infection.* J Acquir Immune Defic Syndr 43:411-417, 2006.

25 Cook J et al. *Effects of alcohol and crack cocaine use on virological and immunological disease progression in a cohort of US women with HIV/AIDS.* 16th IAC, Toronto, 2006.

26 Baum M et al. *Alcohol use accelerates HIV disease progression.* AIDS Res Hum Retrovir 26(5), 2010 (Epub ahead of print).

27 Cook R et al. *Problem drinking and medication adherence among persons with HIV infection.* J Gen Intern Med 16:83-88, 2001.

28 Hendershot C et al. *Alcohol use and antiretroviral adherence: review and meta-analysis.* J Acquir Immune Defic Syndr 52(2):180-202, 2009.

29 Lazo M et al. *Patterns and predictors of changes in adherence to highly active antiretroviral therapy: longitudinal study of men and women.* Clin Infect Dis 45(10):1377-1385, 2007.

30 Kalichman S et al. *Prevalence and clinical implications of interactive toxicity beliefs regarding mixing alcohol and antiretroviral therapies among people living with HIV/AIDS.* AIDS Patient Care STDS 23(6):449-454, 2009.

31 Kalichman S et al. *Alcohol use and sexual risks for HIV/AIDS in sub-Saharan Africa: systematic review of empirical findings.* Prev Sci 8(2):141-151, 2007a.

32 Kalichman S et al. *Randomized trial of a community-based alcohol-related HIV risk-reduction intervention for men and women in Cape Town South Africa.* Ann Behav Med 36(3):270-279, 2008b.

staying free of hepatitis c [page eight]

1 Marincovitch B et al. *Absence of hepatitis C virus transmission in a prospective cohort of heterosexual serodiscordant couples.* Sex Transm Infect 79:160-162, 2003.

2 Gotz HM et al. *A cluster of acute hepatitis C virus infection among men who have sex with men – results from contact tracing and public health implications.* AIDS 19: 969-974, 2005.

3 Rauch A et al. *Unsafe sex and increased incidence of hepatitis C virus infection amongst HIV-infected men who have sex with men: the Swiss Cohort Study.* Clin Infect Dis 41 (online edition), 2005.

4 Ghosn J et al. *Increase in HCV incidence in HIV-1-infected women and men followed in the French PRIMO cohort.* 13th CROI, Denver, abstract 843, 2006.

5 Matthews GV et al. *Further evidence of HCV sexual transmission among HIV-positive men who have sex with men: response to Danta et al.* AIDS 45: 2112-2113, 2007.

6 Fierer DS et al. *Liver fibrosis during an outbreak of acute hepatitis C virus infection in HIV-infected men: a prospective cohort study.* J Infectious Diseases 198:683–686, 2008.

7 Danta M et al. *Evidence of international transmission of HCV in pan-European study of HIV-positive men who have sex with men (MSM).* 4th IAS Conference, Sydney, abstract TUAB201, 2007.

8 Giraudon I et al. *Increase in diagnosed newly acquired hepatitis C in HIV-positive men who have sex with men across London and Brighton, 2002–2006: is this an outbreak?* Sex Transm Infect 84:111–116, 2008.

9 Ruf M et al. *Setting up an enhanced surveillance of newly acquired hepatitis C infection in men who have sex with men: a pilot in London and South East region of England.* Euro Surveill 13(47):pii=19042, 2008. Available online: www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19042

10 Danta M et al. *Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours.* AIDS 11;21(8):983-91, 2007.

11 Turner JM et al. *Behavioural predictors of subsequent hepatitis C diagnosis in a UK clinic sample of HIV-positive men who have sex with men.* Sex Transm Infect 82: 298–300, 2006.

hiv-positive women in clinical trials: a gap in the facts

Sharon L Walmsley is one of a group of female physicians, experts and patient advocates who together set up *Women for Positive Action*, an organisation that campaigns for better inclusion of women's needs into HIV research and care. Here she argues that women's under-representation in clinical trials contributes to ignorance of issues affecting women, and how to address them.

Women currently represent half of all people who live with HIV globally, and that proportion is increasing in some world regions. Yet women are considerably under-represented in HIV clinical trials: since 2000, only 20% of participants in clinical trials of antiretroviral therapy (ART) were women and the proportion has declined in the past 8 years.[1]

This leaves a significant gap in understanding of women and HIV, which is discussed in a recently published opinion piece by Women for Positive Action.[2]

The risk to the foetus of maternal medication in pregnancy, exemplified by thalidomide in the 1950s and 1960s, has dominated discussions about the enrolment of women into clinical trials. In the United States, the Food and Drug Administration forbade women from participating during the early stages of pregnancy following this tragedy. The repercussions meant that many women were precluded from clinical trials.

More recently, the need to include more women in clinical trials has been given greater attention in order to have sample sizes large enough to take participant's sex into account. However, it is clear that the balance has not yet been achieved.

Low female representation in clinical trials over the past ten years is significant not only because half of all people living with HIV are female, but also because women may respond differently to both the disease and ART than men do. For example, women have been consistently shown to have lower viral loads than men at similar stages of HIV infection, most markedly early on, following HIV seroconversion.[3] However, the cause and significance of viral load differences remain unclear.

In addition, it has been suggested that women may respond better to ART than men: in one study, women had better CD4-count responses to therapy and lower death rates, though they experienced more drug-related side-effects.[4] However, existing studies don't provide a clear picture about the use of ART among women.

Women's physical make-up is different to men's: they have a lower body mass, higher body-fat content and hormonal differences. Adverse effects and the ability to tolerate certain antiretroviral drugs may differ in women. Birth control pills, hormone replacement therapy and pregnancy could also alter the effects of HIV medications. Without data investigating the impact of these on treatment in women with HIV, potential improvements to the lives of millions of women are impeded.

Some HIV clinical trials have been successful in increasing women's participation. For example, 38% of participants in the STEP trial, which aimed to find a preventive HIV vaccine, were women. The GRACE Study[5] was specifically designed to assess sex-based differences in the efficacy and safety of darunavir boosted with ritonavir. To achieve the recruitment goal of 420 patients (approximately 70% female), each study site was required to enrol three women before enroling a man. Of the 429 people living with HIV enroled, 287 were women.

It reported similar treatment response rates between men and women, but over a third of women dropped out of the trial compared with under a quarter of men; some discontinuations may represent challenges unique to women in clinical trials. For future studies, the authors highlighted the importance of addressing the unique needs of women during the screening process and throughout, to optimise study retention.

According to the founder and Chair of The Well Project, Dawn Averitt Bridge, "GRACE sets a new standard for how future HIV studies should be conducted, as we now know that treatment-experienced women... can and will successfully participate in clinical trials if the studies are designed and supported in the right way."

Given these recent successes, how can we continue to ensure that more women are included in HIV clinical trials? Researchers, physicians and clinical trial

sponsors all need to take action in order to address the imbalance.

Professor Jane Anderson, HIV consultant physician at Homerton University Hospital, London, elaborates: "The under-representation of women in HIV-related clinical trials falls into three main areas: the study design and protocol, increasing the participation of women in trials and raising awareness across the HIV field that more studies and data analysis is needed in women."

Clinical researchers need to ensure equal sex representation in the early stages of drug development. At the same time, clinical trials should be designed to give meaningful data on sex-related differences and remove unfair barriers to female participation. For example, the provision of childcare and other social support can often be seen as unaffordable or unnecessary, but these can be critical to women's participation.

Including women in the planning stages of clinical trials will allow these issues to be raised. Furthermore, physicians should work closely with investigators to support the inclusion of women, and clinical trial sponsors should find ways to collaborate with centres and investigators that treat a high proportion of HIV-positive women.

"More women should be involved in the planning and implementation of studies to ensure the needs of female participants are considered," notes Professor Margaret Johnson, consultant physician at London's Royal Free Hospital. "Women living with HIV must also understand the importance of them volunteering to participate in clinical trials. What we learn from women today can be applied to women's care in the future."

Beyond researchers and doctors, the national and supranational regulatory authorities can have a positive effect on women's representation in clinical trials. Journals that publish HIV research and conference organisers also play significant roles in drawing attention to the importance of the issue: editors and organisers should encourage submissions focusing on women and include female health specialists on editorial and conference boards.

Improving women's health is not only a women's issue. As the GRACE study in the United States proved, by learning more about how women respond to HIV treatments and by improving their total quality of care, we can not only improve their quality of life but also that of their partners, children and communities.

Winnie Ssanyu-Sseruma of Christian Aid believes that "Encouraging the participation of community representatives in the planning and implementation of trials is vital. Community involvement at all levels is essential if we are to enrol more women in clinical trials."

Leaders in medicine, research, public health and communities can improve the lives of women living with HIV, but specific data on the effects of treatments will be essential. Together, we need to ensure that women around the world can benefit from the knowledge gained through HIV clinical trials. ■

Women for Positive Action is a global initiative established in response to the need to address specific concerns of women living and working with HIV. The group is made up of healthcare professionals, women living with HIV, and community group representatives from across Canada, Europe and Latin America.

Women for Positive Action aims to empower, educate and support women with HIV and the professionals and community advocates/leaders involved in their treatment. The group explores issues facing women with HIV and provides meaningful education-based support to respond to these needs and to contribute towards an enhanced quality of life for women with HIV. For further information, please visit www.womenforpositiveaction.org.

Women for Positive Action acknowledge the contribution of Winnie Ssanyu-Sseruma in the preparation of this article.

references to articles *(from page 13)*

12 Fierer DS et al. *Characterization of an outbreak of acute HCV infection in HIV-infected men in New York City.* 16th Conference on Retroviruses and Opportunistic Infections, Montreal, abstract 802, 2009.

13 Aizen K et al. *Acute hepatitis C (HCV) in a cohort of HIV-positive homosexual men – patient characteristics, risk factors and outcomes.* 9th Annual Meeting of the British HIV Association, Manchester, abstract P45, 2003.

14 Danta M et al. *Evidence for sexual transmission of HCV in recent epidemic in HIV-infected men in South-East England.* 56th Annual Meeting of the American Association for the Study of Liver Diseases, San Francisco, abstract 67040, 2005.

15 Turner JM et al. *Behavioural predictors of subsequent hepatitis C diagnosis in a UK clinic sample of HIV-positive men who have sex with men.* Sex Transm Infect 82: 298-300, 2006.

16 E.g. Leruez-Ville M et al. *Detection of hepatitis C virus in the semen of infected men.* Lancet 356: 42–43, 2000.

17 Turner J et al. *Hepatitis C viral load in semen of HIV-positive men during acute and chronic hepatitis infection.* 2nd Joint BHIVA/BASHH Conference, Manchester, abstract 05, 2010.

18 Danta M et al. *Evidence for sexual transmission of HCV in recent epidemic in HIV-infected men in the UK.* 13th CROI, Denver, abstract 86, 2006.

19 Schmidt AJ et al. *The trouble with bleeding: why do HIV-positive gay men get hepatitis C?* 12th European AIDS Conference, Cologne, BPD 1/7, 2009.

20 Fox J et al. *Increasing incidence of acute hepatitis C in individuals diagnosed with primary HIV in the United Kingdom.* AIDS 22: 666–668, 2008.

21 Owen, G *An 'elephant in the room'? Stigma and hepatitis transmission among HIV-positive 'serosorting' gay men.* Culture, Health and Sexuality 10: 601–610, 2008.

hiv-positive women in clinical trials [page fourteen]

1 Struble K et al. *Meta-analysis of efficacy outcomes for treatment-naïve and treatment-experienced HIV-infected women in randomized controlled clinical trials: 2000 to 2008.* 16th CROI, Montreal, abstract 987b, 2009.

2 d'Arminio Monforte A et al. *on behalf of Women for Positive Action Better mind the gap: addressing the shortage of HIV-positive women in clinical trials.* AIDS 24:1091–1094, 2010.

3 Gandhi M et al. *Does Gender Influence HIV Viral Load?* 9th CROI, Seattle, abstract 775-W, 2002.

4 Collazos J et al. *Sex differences in the clinical, immunological and virological parameters of HIV-infected patients treated with HAART.* AIDS 21: 835–843, 2007.

5 Squires K et al on behalf of the GRACE (Gender, Race And Clinical Experience) Study *48-Week results of Darunavir/r-based therapy in the largest trial in North America to focus on treatment-experienced women.* 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Cape Town. Abstract MOPEB042. 2009.

news in brief [page twelve]

slow progress to routine tests

1 Perry N et al. *HIV testing in acute general medicine admissions must be universally offered to reduce undiagnosed HIV.* 2nd BHIVA/BASHH joint conference, Manchester, abstract 019, 2010.

2 Gupta N et al. *Audit of HIV testing in a district general hospital.* 2nd BHIVA/BASHH joint conference, Manchester, abstract P282, 2010.

3 Read PR et al (presenter Fox J). *Community and hospital HIV testing in the highest HIV prevalence area in the UK; missed opportunities for earlier diagnoses identified.* 2nd BHIVA/BASHH joint conference, Manchester, abstract 021, 2010.

sharp increase in lgv cases

1 Powers C et al. *Substantial increase in cases of lymphogranuloma venereum (LGV) in the UK. 2nd* BHIVA/BASHH joint conference, Manchester, 2010 (no abstract submitted).

zinc helps cd4 counts

1 Baum MK et al. *Randomized, controlled clinical trial of zinc supplementation to prevent immunological failure in HIV-infected adults.* Clin Infect Dis 50: online edition, 2010.

hepatitis c in semen unlikely to explain transmission

1 Turner J et al. *Hepatitis C viral load in semen of HIV-positive men during acute and chronic hepatitis infection.* 2nd BHIVA/BASHH joint conference, Manchester, abstract 05, 2010.

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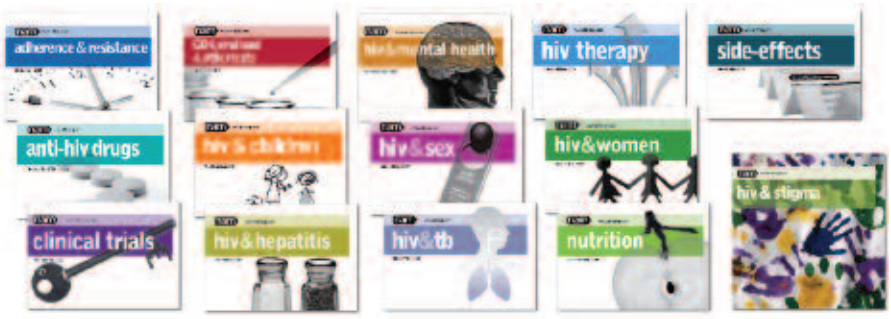

If you have ever used NAM's patient information booklets, please help us make sure they continue to be useful, by filling in the questionnaire below:

Which of the following booklets have you read/used (option to tick more than one)

- ❒ adherence and resistance
- ❒ CD4, viral load and other tests
- ❒ hiv & children
- ❒ hiv & mental health
- ❒ hiv & stigma
- ❒ hiv & women
- ❒ nutrition
- ❒ anti-hiv drugs
- ❒ clinical trials
- ❒ hiv & hepatitis
- ❒ hiv & sex
- ❒ hiv & tb
- ❒ hiv therapy
- ❒ side-effects

As a result of reading this/these resources have you learnt anything about HIV, your health and treatment?

- ❒ I have learnt nothing new
- ❒ I have learnt something but it's not particularly useful to me
- ❒ I have learnt something that is useful to me
- ❒ I have learnt something that seems vitally important to me

As a result of using these resources I am more likely to: (tick all that apply)

- ❒ Discuss treatment and care with my healthcare team
- ❒ Feel more confident talking to my healthcare team
- ❒ Feel better equipped to take decisions regarding my treatment and care
- ❒ Feel more informed about HIV treatment and living well with HIV
- ❒ Find other information and support, if I need it
- ❒ None of the above

Have you ever passed on a booklet to another person or told them about these resources?

❒ Yes ❒ No

I am: ❒ male ❒ female ❒ transgender

I live: ❒ in London ❒ in the UK but outside of London ❒ outside of the UK

My ethnic background is:
❒ White ❒ Black-African
❒ Black Caribbean ❒ Black – other
❒ Indian or Pakistani or Bangladeshi
❒ other Asian or oriental ❒ other or mixed

My HIV status is: ❒ unknown ❒ negative ❒ positive

The information you have given is confidential and will only be used by NAM to help us assess the reach, availability and relevance of the information booklets.

Many thanks for filling in this questionnaire.

Please return to: NAM, freepost, LON17995, London SW9 6BR
or return in the freepost envelope provided

JUNE10

thanks to our funders

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where to find out more about hiv

- **Find out more about HIV treatment:**
  NAM's factsheets, booklets, directories and website keep you up to date about key topics, and are designed to help you make your healthcare and HIV treatment decisions. Contact NAM to find out more and order your copies.
- **www.aidsmap.com**
  Visit our website for the latest news about HIV & AIDS, a fully searchable treatments database and a complete list of sexual health clinics in the UK.
- **THT Direct**
  Offers information and advice to anyone infected, affected or concerned about issues relating to HIV and sexual health.
  0845 1221 200
  Mon-Fri, 10am-10pm Sat-Sun, 12pm-6pm
- **i-Base Treatment Phoneline**
  An HIV treatment phoneline, where you can discuss your issues with a treatment advocate.
  0808 8006 013
  Mon-Wed, 12pm-4pm