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in this issue

The British HIV Association (BHIVA) has had a busy time of things recently, with the issuing of its new draft guidelines for the treatment of HIV-infected adults and its Fourteenth Annual Conference in Belfast. Still, it's given HTU a wealth of news to discuss and reminds us just how quickly things are moving in this field.

Our knowledge of antiretrovirals grows at an astounding rate, resulting in new guidelines and new approaches but also new warnings. With the longer life that current treatment options bring, we are finding out more about the long-term effects of HIV and the drugs used to treat it. This inevitably raises some concerns, as does any research looking at people who are getting older. But, as we said back in December when we focused on cancer risk, people with HIV benefit from more regular health monitoring than many others in the UK. This month we're looking at the risk of heart problems, and it's reassuring to know that monitoring can predict risk and prompt changes that will have huge benefits.

And there's more good news. We're pleased to say that this issue is not all about antiretrovirals. One topic that comes up again and again is whether we can hope for something better than lifelong daily therapy for people with HIV. With reports on a novel approach to treatment and ongoing vaccine research, it's clear that some studies are pushing for more.

page 3 When faced with an HIV-positive leukaemia patient, a group of German scientists decided that ridding his body of the cancer was not enough. By replacing the cancerous immune system with one already genetically resistant to HIV, could they eliminate the virus as well?

page 4 Since before the introduction of Highly Active Antiretroviral Therapy (HAART), the possibility of heart problems in those with HIV has caused concern. In *HAART to Heart* HTU reviews the current data to find out if HIV, or the drugs used to treat it, can influence the risk of heart disease.

page 8 HIV specialists are asked to deal with many health concerns. Not only is monitoring of the virus required but also vigilance when it comes to associated conditions. With cardiovascular disease being the focus of HTU, we ask the clinics to take *Heart in their hands*.

page 12 Not only do we have the usual mix of treatment-related *News in brief*, there's also a chance for you to get involved. With reports of a public consultation on the new British HIV Association guidelines and a call for couples for vaccine research, your participation could make a real difference.

page 14 The Crown Prosecution Service has finally released its guidelines on prosecutions of intentional or reckless HIV transmission. While some have praised the much needed clarification contained in the guidelines, there remain fears that some aspects of the law in this area are open to interpretation.



hiv treatment update

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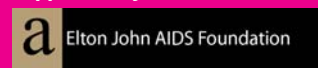
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stem cell transplant raises hope

by Rob Dawson

Scientists have been trying to find ways of eradicating HIV from the body, ever since the virus was first discovered, so far without success. Without daily anti-HIV drugs, hidden reservoirs of the virus can begin to replicate and overpower the immune system. The majority of today's research into HIV treatment focuses on these antiretroviral drugs, as other avenues of exploration have tended to be fruitless. However, a German study presented at the 15th annual Conference on Retroviruses and Opportunistic Infections (CROI) in Boston serves as a reminder that we should never stop looking for innovative approaches.

Scientists have long considered the possibility that cell transplants could offer people with HIV healthy, HIV-free blood cells. Bone marrow produces new blood cells so bone-marrow transplants provoked initial interest. However, a recent study showed that eradication of HIV by this method was unlikely; when antiretroviral therapy was stopped after the bone-marrow transplant, the virus soon became detectable.¹

Rather than trying to rid the body of HIV, other types of transplant have tried to replenish damaged immune systems. Stem cells are cells which have the potential to develop into any other kind of cell type. Healthy donor stem cells are transplanted into the damaged immune system where they develop into new immune cells. The benefits of these transplants had been dismissed by many, but a presentation by Dr Gero Hütter, from the Medical University of Berlin,² has renewed interest.

In his single-patient study, a 40-year-old man who had been living with HIV since

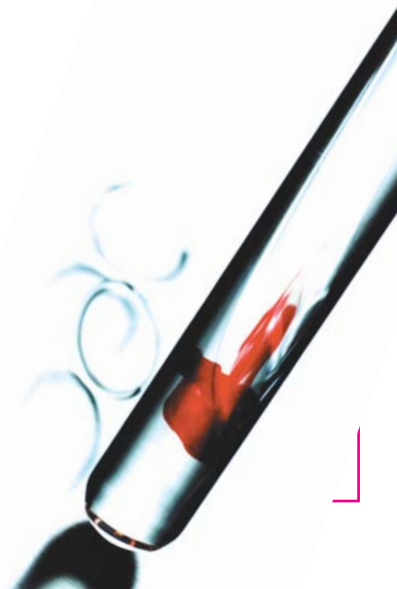
1995 suffered a relapse of leukaemia, a cancer of the immune cells. After intensive chemotherapy to remove the cancerous cells, a stem cell transplant was necessary to replace them with healthy ones. Rather than simply focusing on treating the patient's cancer, Dr Hütter went one step further and attempted a transplant that would increase the patient's chances of surviving HIV too. The stem cells used in the transplant were provided by a donor whose immune system was already genetically resistant to HIV.

HIV commonly uses a receptor called CCR5 as a doorway into immune cells. People who lack this receptor are highly resistant to HIV infection. We inherit two copies of the gene that makes this receptor, one from each of our parents. If the copies from both parents are defective, a person is highly resistant to HIV infection or, if infected, rarely progresses to advanced HIV infection and so may not need anti-HIV drugs. The German researchers hoped that by using stem cells from a donor with this receptor-disabling genetic defect, the newly restored immune cells might better resist HIV infection and replication.

So far, that appears to be exactly what is happening. Researchers told the patient to stop taking his anti-HIV drugs on the day of the transplant and he has not restarted them. Sixty-one days after the transplant, the level of HIV in his blood fell below the limit of detection and has remained there. Researchers can no longer find evidence of the virus's genetic material in cells in the blood, bone marrow or rectum. These sensitive tests have remained negative for over 285 days.

The doctors involved have been rightly cautious of talking about a cure. Follow-up of the case is important as HIV could still be hiding somewhere in the patient's body. If the hidden virus utilises an alternate receptor to CCR5, known as CXCR4, viral load could rebound. It's also a complicated procedure requiring a lengthy hospitalisation and can cause numerous and potentially life-threatening side effects. The doctors need to destroy a person's existing immune system with a potentially lethal course of chemotherapy and radiation before the transplant, so post-transplant survival is never a sure thing. We also have to remember that this is only one patient.

Nevertheless, the study has generated excitement. At the very least, it reinforces the importance of trying to eliminate or disrupt the CCR5 receptor. It could fuel other experimental approaches, such as gene therapy, that disrupt the genes responsible for producing CCR5 receptors. And some optimistic doctors have even suggested that the approach could be a possible future treatment for those very rare cases where all current and experimental antiretrovirals fail. ■





haart to heart

Cardiovascular disease (disease involving the heart and/or blood vessels) is an increasing problem in modern society and the biggest killer in the UK. With supermarket food labels reminding us to cut down on fat and smoking now banned in public places, it's clear that the government is working aggressively to minimise the death toll. While this will help to reduce the risk for many, should people with HIV be making greater efforts to ward off heart problems?

In the past, cardiovascular problems were less common in those with HIV when compared with the general population, but this was due to the greatly reduced life expectancy that went hand-in-hand with a diagnosis. Now that improved therapies bring longer life, diseases of older age are more prominent. Heart disease and stroke have become leading causes of death in people with HIV, as they are in the general population, and current research hopes to determine just how the virus, and the drugs that manage it, affect cardiovascular health.

Analyses of cohort studies and hospital administrative databases suggest that those with HIV appear to be at an increased risk of CVD (around two-fold)¹ when compared to the general population. However, the total risk is still small and is more than offset by the reduction in HIV-related complications resulting from antiretroviral therapy.² The main causes of this increased cardiovascular risk fall into three categories: those that are an inherent part of HIV infection; those that are treatment-related; and those that are lifestyle-related.



HIV's attack

The possibility that HIV infection itself could play a role in the development of CVD was noted before the advent of combination antiretroviral therapy, due to irregular levels of fats seen in the blood of people infected with the virus. These changes in blood fats (known as dyslipidaemia) can affect the risk of developing CVD in a number of ways. Cholesterol and triglycerides are both body fats (lipids) and having abnormal levels of these can cause narrowing of the arteries (atherosclerosis), heart attacks, strokes and coronary heart disease. Not all types of cholesterol are 'bad'; a form of 'good' cholesterol (high density lipoprotein or HDL) can be beneficial. It is the proportion of 'bad' cholesterol (low density lipoprotein or LDL) to 'good' cholesterol that influences the likelihood of cardiovascular problems.

A reduction in the beneficial type of cholesterol has been seen in people with HIV. In men in the Multicenter AIDS Cohort Study (MACS), investigators found that acquiring HIV was associated with a decline in total cholesterol, including the cardioprotective HDL.³ In HIV-positive women who are not taking anti-HIV drugs, low levels of HDL have also been accompanied by high triglyceride levels – both risk factors for CVD.⁴

HIV infection may also result in endothelial damage (damage to cells that line the heart and blood vessels), which can cause blood vessels to function abnormally.⁵ A disturbance of blood vessels in this way is considered key to the development of cardiovascular disease, as it leads to narrowing of the arteries. It can be measured by looking at the amount a vessel expands when blood flow

increases through it and is known as flow-mediated dilatation (FMD). This indicator of early CVD has been shown to improve rapidly when patients initiate antiretroviral therapy, indicating that HIV itself is damaging to these vessels.⁶ This vessel damage may be caused by the inflammation-causing chemicals induced by HIV (inflammatory cytokines).⁷

The status of the immune system also appears to be linked to cardiovascular risk. In the Strategic Management of Antiretroviral Therapy (SMART) study, investigators hoped that interrupting treatment for a short time would help to reduce the burden and potential adverse effects of lifelong therapy. Instead, the trial had to be stopped because treatment interruption not only raised the risk of developing AIDS-defining illnesses, but also increased the likelihood of cardiovascular disease and other serious illnesses.⁸ Individuals who interrupted treatment had a 60% higher risk of cardiovascular disease during a 16-month follow-up period. Some of this heightened risk may be attributable to higher amounts of HIV in the blood and greater immune damage (as measured by lower CD4 cell counts), because even in those SMART study participants who weren't taking antiretrovirals at the start of the study, delaying therapy (until the CD4 count had decreased) was associated with increased CVD compared with those who started treatment immediately upon study enrolment.⁹

Similar findings were seen in the Flexible Initial Retrovirus Suppressive Therapies (FIRST) study. Although the main aim of the study was to evaluate different antiretrovirals, a subsequent analysis found that a lower CD4 cell

quick reference keywords

atherosclerosis narrowing of the arteries.

cardiovascular disease (CVD) disease that involves the heart or blood vessels.

cholesterol a type of body fat. The ratio of 'bad' cholesterol (low density lipoprotein or LDL) to 'good' cholesterol (high density lipoprotein or HDL) influences the likelihood of cardiovascular problems.

dyslipidaemia abnormal changes in body fats.

endothelium cells that line the heart and blood vessels.

flow-mediated dilatation (FMD) measures the amount a vessel expands when blood flow increases through it in order to pick up early cardiovascular problems.

framingham score used to estimate the risk of having a heart attack within the next ten years.

lipids body fats.

triglyceride a type of body fat. High levels increase the likelihood of cardiovascular problems.



count was associated with a higher risk of cardiovascular events.¹⁰

The data from both the SMART and FIRST studies suggest that controlling HIV replication and maintaining a high CD4 cell count plays an important role in reducing the likelihood of CVD.

The antiretroviral affect

The extent to which combination antiretroviral therapy influences the risk of cardiovascular problems is a topic that stirs debate. Investigators from the US Department of Veterans Affairs stand by a claim they made in 2003 – that antiretroviral therapy has a “negligible public health risk” of cardiovascular events.² After repeating a retrospective analysis of records from over 41,000 people receiving HIV treatment and care and extending the analysis period by two-and-a-half years, they found that antiretroviral therapy reduced the risk of death from any cause without increasing the risk of heart attack, heart bypass surgery or death due to serious cardiovascular events.

Other studies suggest that the increased risk of CVD caused by anti-HIV drugs is, at most, moderate. Researchers using the Danish HIV Cohort Study, which records data from all Danish HIV-positive patients, quantified the increased risk of ischaemic heart disease (characterised by reduced blood supply to the heart) as “of the same order as that introduced by smoking 1–4 cigarettes per day”. They also suggested that the risk does not increase with longer duration of therapy.¹¹

PIs and lipid changes Contrary to these findings, the D:A:D (Data Collection on Adverse Effects of Antiretroviral Drugs) study paints a darker picture. In 2005, the D:A:D study reported that each additional year of antiretroviral therapy boosts

the risk of heart attack and recently they attributed the increased risk to protease inhibitors (PIs).¹² To analyse the frequency of heart attacks in people exposed to antiretrovirals, the observational D:A:D study reviewed data covering three continents. During 94,469 person-years of follow-up, 345 people had a heart attack. Each additional year of exposure to PIs resulted in a 16% increased risk of heart attack.

While an increase of this magnitude sounds high, it’s worth noting that the overall frequency actually remained low. The figures are a measure of the increase in risk, not a measure of the actual risk of getting a heart attack. For example, if there was a 16% increase in risk after taking PIs for a year and there was a 5% chance of getting a heart attack previously, there would be an increase of 16% of the 5%, or 0.8% after one year.

However, the D:A:D data showed that the cumulative risk can add up over time. The study authors likened the increased cardiovascular risk after five years of PI-based therapy to the increased risk attributable to having diabetes mellitus (an increase of around 50%).

Interestingly, adjusting the results to take into account lipid changes didn’t completely eliminate the association. This could suggest that the PIs used in this study might also be affecting CVD risk through some other mechanism. It is unknown whether the adverse effects of PIs seen in D:A:D would be observed with more recently approved PIs such as atazanavir (which has minimal effects on lipids) or with use of lower-dose ritonavir boosting strategies.

Commenting on the findings in an editorial accompanying the data, James

Stein, Associate Professor in the Division of Cardiovascular Medicine at the University of Wisconsin, counselled against unnecessary panic. He said, “This risk of cardiovascular disease would be considered low or at most moderate, depending on a patient’s risk factor burden. Thus there does not seem to be an epidemic on the horizon – simply a risk that needs to be managed.”

Findings from the AIDS Clinical Trials Group (ACTG) seem to agree. Their 5152s study failed to demonstrate an association between PI-containing therapy and impaired flow-mediated dilatation (the early marker of artery narrowing and predictor of CVD).⁶

However, protease inhibitors have long been linked with changes in blood fats that could increase the risk of CVD, most strikingly with ritonavir. By administering low-dose ritonavir either once daily or twice daily to non-smoking, HIV-negative individuals, researchers have tried to define ritonavir’s effect. After 14 days of receiving ritonavir, individuals in the once-daily arm experienced a 6% decrease in HDL cholesterol (the beneficial variety), whereas those in the twice-daily arm experienced a 10% decrease in HDL and a 32% increase in triglycerides.¹³

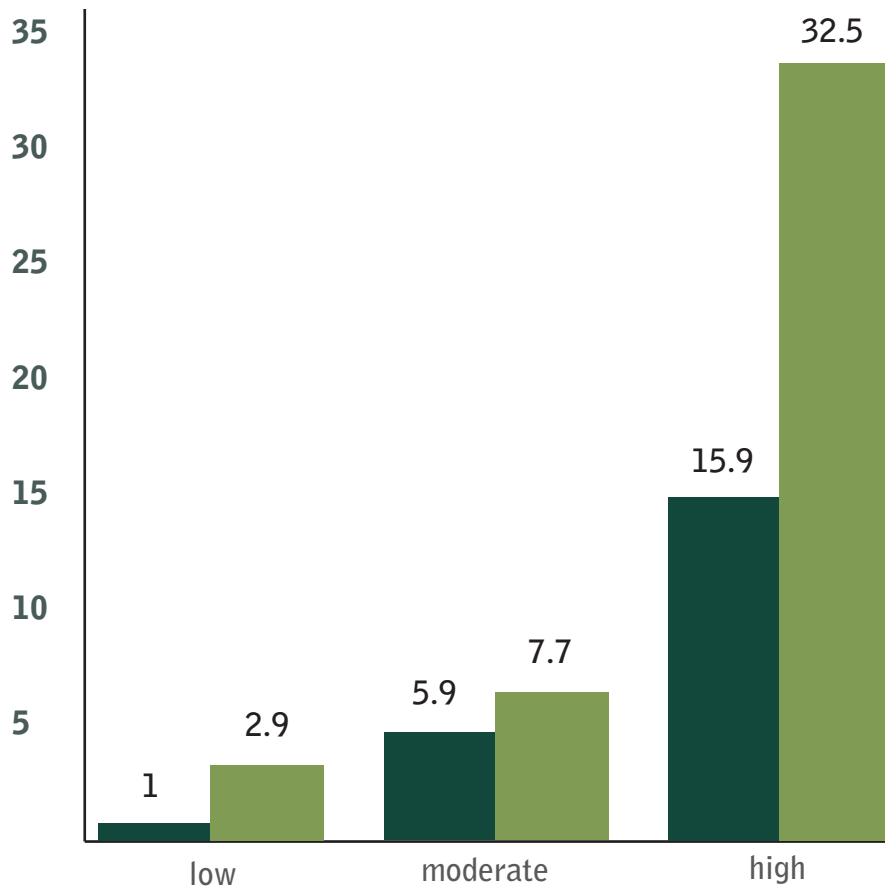
Other drug classes

While some NRTIs, most notably stavudine, have been shown to adversely influence lipids, the D:A:D study did not find any link between either stavudine or zidovudine and cardiovascular risk.¹⁴ However, the study did find a surprising association between recent (although not past) use of either abacavir or didanosine and an increased risk of heart attack: abacavir use nearly doubled the risk, while risk rose by around 50% with didanosine use. For most patients these findings do



Figure 1: Comparing recent use with no recent use of abacavir: rate of heart attacks for those with low, moderate, and high risk of coronary heart disease¹³

Predicted 10-year risk of coronary heart disease



not push them into a high risk CVD category. The risk will be most relevant for anyone who is already at high risk of having a heart attack (see figure 1), in which case, any modifications that could reduce the likelihood of cardiovascular problems should be considered, including changing treatments and stopping smoking.

The US Food and Drug Administration (FDA) highlighted the need for further research regarding the D:A:D findings as “incomplete” because they did not include an analysis of abacavir’s competitor, tenofovir, nor another important antiretroviral drug, emtricitabine.

Among the NRTIs in general, newer agents seem to be associated with fewer lipid abnormalities than older agents. In the GS 934 study, which compared a regimen containing zidovudine and lamivudine versus tenofovir and emtricitabine (both with efavirenz as the third agent), significantly greater

increases in cholesterol and triglycerides were observed in the zidovudine arm.¹⁵ Similar results have been seen in comparisons of stavudine and tenofovir.¹⁶

In the non-nucleoside reverse transcriptase inhibitor (NNRTIs) class, the lipid effects of efavirenz and nevirapine were compared in the 2NN study. The results demonstrated significantly greater increases in ‘bad’ LDL cholesterol levels and triglycerides in the efavirenz arm, whereas subjects in the nevirapine arm demonstrated greater ‘good’ HDL cholesterol increases.¹⁷ The D:A:D study found no evidence of increased cardiovascular risk with NNRTIs but pointed out that the length of observation for exposure to this class of drug was less than for PIs, where an association was found.

Insulin resistance

Insulin resistance occurs when increased levels of insulin are required by the body. It’s associated with the development of diabetes mellitus and

increased cardiovascular risk. Some antiretroviral agents have been linked to insulin resistance, but further research is needed. Although PIs are thought to play a part, data from the MACS study found that cumulative exposure to PIs was not associated with insulin resistance.¹⁸ They did find that each additional year of exposure to NRTIs was associated with significant increases in the development of insulin resistance and a comparison of individual agents found stavudine to have the greatest impact.

Indinavir is a PI that has been associated with the development of insulin resistance, not only in studies of patients with HIV, but also in a 4-week study performed in HIV-uninfected individuals.¹⁹ Regimens containing zidovudine and lamivudine have also been shown to contribute to insulin resistance.²⁰

Healthy life for a healthy heart

While antiretrovirals may influence the body’s metabolism and blood fats, managing HIV is the first priority. So rather than focusing intently on anti-HIV drugs and any moderate increases in CVD risk, focusing on lifestyle may provide greater benefits.

The main risk factors for CVD in people with HIV are the same as those for the general population, including smoking, hypertension, diabetes, obesity, and dyslipidemia (lipid changes). While several of these risk factors are more common in people with HIV, most are still modifiable.

Smoking

Looking again at the D:A:D study, high rates of several of these CVD risk factors were seen, in particular smoking.¹² At the start of the study, 51.5% of participants were current smokers, 22.2% had elevated total cholesterol, and 25.7% had low levels of HDL cholesterol. Smoking was associated with a 2.83-fold increase in the relative risk of CVD.

In the US, a recent analysis of cardiovascular risk in the MACS and the Women’s Interagency HIV Study (WIHS) found that 35% to 40% of

those with HIV were current smokers, a rate higher than in uninfected participants.²¹ In addition, HIV-positive gay men are not only more likely to smoke, but are more likely than other gay men to be heavy smokers, smoking 10 or more cigarettes per day.²²

Most doctors agree that quitting smoking is the single most important step in reducing CVD risk. If you go smoke-free, the NHS says that you are up to four times more likely to succeed if you use a support service and nicotine replacement, such as patches or gum, to manage cravings. The new stop-smoking drug *Champix* can be taken alongside antiretrovirals and may also help people quit.

Diet

Another modifiable risk factor is obesity. Indirectly associated with obesity is diabetes mellitus, a condition also associated with HIV in several studies, especially when hepatitis C infection is also present.²³ In the MACS study, the incidence of diabetes was four times higher in the 568 men with HIV on antiretroviral therapy than in the 710 HIV-negative participants.¹⁸

While it's easy to look to antiretrovirals for an answer, diet and exercise are important factors. Raised lipid levels in people with HIV have

GMFA's latest campaign highlights smoking risks



been attributed to a higher fat diet. In one study, those with HIV consumed more total fat, more saturated fat and more cholesterol than the general population, even though their total calorie intake was no different.²⁴ The researchers conclude: "Careful assessment of dietary intake and more aggressive dietary intervention may prove to be beneficial to the prevention of cardiovascular disease."

Healthier meal choices can lead to better outcomes, and diets high in fibre have been associated with higher HDL levels and reduced fat deposition in people with HIV.²⁵ Making these dietary changes can be difficult, but HIV clinics can help; regular dietary counselling has been shown to have beneficial effects on blood fat levels. A randomised Brazilian study found that HIV-positive people who received regular dietary counselling after starting antiretroviral therapy were significantly less likely to experience lipid elevations on treatment when compared with people receiving one-off nutritional advice.²⁶ The study author stressed that this type of intervention should be incorporated into the clinical care of individuals when they start antiretroviral therapy rather than waiting until lipid changes have been identified.

Exercise can also reduce cardiovascular risk in people with HIV and a trend toward increased HDL levels with moderate to heavy aerobic exercise has been observed.²⁷ Greater benefits have also been seen when pharmaceutical intervention for cardiovascular risk are combined with exercise, rather than using drugs alone.²⁸

Drugs

Other risk factors may also play a part. While US investigators found a high prevalence (15%) of narrowing of

the arteries amongst HIV-positive African-Americans, they were only able to attribute 1.6% of cases to the use of antiretroviral therapy.²⁹ Traditional risk factors caused the majority of problems and many of the patients were also long-term cocaine users, a behaviour that has been associated with an increased risk of CVD.

While drugs like cocaine and crystal meth have been linked to an increased risk of cardiovascular problems in the general population, the area is still under-researched in people with HIV. Cocaine alone did magnify cardiac mass and mortality in a mouse model of AIDS³⁰ and US researchers have proposed that HIV and cocaine may work hand-in-hand to hamper cardiac function.³¹ When you consider the fact that some groups of people with HIV (such as HIV-positive gay men) are more likely to use recreational drugs than their HIV-negative counterparts,²² the results are a cause for concern.

Screening

Thankfully, with regular monitoring, it's possible to identify those at higher risk of CDV. Reaching the cholesterol targets recommended for the general population can help to decrease long-term cardiovascular risk for people with HIV.

Tools are available to calculate individual cardiovascular risk, such as the Framingham equation which estimates an individual's chance of having a heart attack in the next ten years. However, some doctors argue that this tool was developed for use in the general population and so may not be as appropriate for use in people with HIV. The Framingham score could be affected by factors related to HIV disease itself which are not captured in the equation, leading to incorrect



top tips for beating heart disease

Minor lifestyle change can make a big difference to your cardiovascular health.

Eat a healthy, balanced diet

Your diet should be low in saturated fat, sugar and salt, and contain plenty of fruit and vegetables (at least five portions a day).

Be more physically active

Exercise is known to increase 'good cholesterol' (HDL). NHS guidelines recommend regular aerobic (cardiovascular) exercise, for a minimum of 30 minutes a day, at least 3-4 times a week.

Give up smoking

Smoking is a major risk factor for developing atherosclerosis (hardening of the arteries).

Reduce your alcohol consumption

The recommended daily amount of alcohol for men is 3-4 units a day, and it is 2-3 units for women.

Keep your blood pressure under control

The average target blood pressure should be below 140/85mmHg. If you have high blood pressure, ask your GP to check your blood pressure regularly.

Keep your diabetes under control

If you have diabetes, it is important to keep control of your blood sugar level. You can reduce your chances of developing diabetes by being physically active, controlling your weight, and keeping your blood pressure under control. If you are diabetic, your target blood pressure level is below 130/80 mmHg.

estimations. Data so far seem to suggest that the Framingham risk equation may slightly under-predict the risk of heart attack in people with HIV who are receiving antiretroviral therapy and may slightly over-predict the risk in HIV-infected patients who are not receiving antiretroviral therapy. However, the D:A:D study group has recently developed a CVD-risk equation specifically for use with HIV.

This risk needs to be put into perspective before making any therapeutic decisions so it can help for patients and doctors to look at the risk for HIV disease progression (EuroSIDA risk score) along with any risk of CVD.

Managing risks

While lifestyle adjustments may well provide reductions in CVD risk, they will not always be enough. The updated British HIV Association guidelines (BHIVA) guidelines for 2008 recommend CVD-risk assessment and lifestyle advice yearly for HIV-positive

people, unless they're switching treatments, in which case assessment should occur both before and 2-4 months after the change. Following the assessment, if a single risk factor (such as smoking) is present, appropriate dietary advice and specific management (such as quitting smoking) should be sufficient. If more than one risk factor is present, then the Framingham or D:A:D equations can be used to calculate the ten-year risk of developing CVD. Based on the outcome, lifestyle advice may still be enough (if the risk is less than 10-20%), though more intensive management may be required. In circumstances where cardiovascular risk remains high, the use of cholesterol lowering drugs (such as statins) or an alternative antiretroviral combination that may not affect lipids can be considered.

Studies have shown that the addition of a cholesterol lowering drug, such as pravastatin, to PI-based therapy has resulted in significant lipid reductions.

³² Some of these drugs cannot be taken with antiretrovirals, so clinical supervision is necessary.

The most commonly studied switch of antiretrovirals to minimise lipid changes involves that of a boosted PI for an NNRTI or an NRTI. Improvements in cholesterol in the 10-20% range have been seen, along with greater improvements in triglyceride levels.³³ Similar improvements have been observed when switching PIs to atazanavir.³⁴

So even where risk does increase, with careful management and consideration of lifestyle choices it's possible for people with HIV to reduce the chances of having a heart attack to low levels. And we should keep these risks in perspective. The rate of non-AIDS-related deaths amongst people with HIV has actually remained relatively flat.³⁵ It's because AIDS-related deaths have declined substantially that non-AIDS-related deaths now receive so much attention.



heart in their hands

The recent flurry of information on cardiovascular risk has further increased the need for clinical vigilance by HIV healthcare professionals. With diseases of ageing becoming evermore important in people with HIV, *HTU* asked healthcare professionals for their views on cardiovascular disease and how the risks can be managed in a clinical setting. Dr Mark Nelson (MN) of London's Chelsea and Westminster Hospital and Nicky Perry (NP), Nurse and Research Manager at the Elton John Centre in Brighton, provided reassuring answers.

HTU: There seems to be a mixed bag of reports linking antiretroviral therapy to heart and circulatory problems. The D:A:D study seems to ring regular alarm bells but a report from the US Department of Veterans Affairs says that any risk is negligible. There is obvious confusion for people living with HIV, but is there cause for concern?

MN: There are several studies looking at HIV and cardiovascular disease which show an increased risk. People with HIV have many risk factors, including preponderance for smoking, hyperlipidaemia associated with antiretroviral drugs, glucose intolerance

and diabetes. Some studies have also seen an excess of hypertension [high blood pressure – a risk factor for cardiovascular disease] related to antiretrovirals. Also, the recent D:A:D study has suggested a direct role for certain drugs, including protease inhibitors and some nucleoside analogues. Individuals need to be aware that they should be screened for risk of heart disease in clinic and have regular blood pressure checks, but should also look at their lifestyle, especially stopping smoking.

HTU: As people with HIV are living longer, can some of the increased risk of cardiovascular disease be related to ageing?

MN: We know that age is a risk factor for cardiovascular disease and many other diseases as well. We now need to make sure that we are not only concentrating on CD4 and viral load. People with HIV should be properly screened and counselled for increased risk of not only cardiovascular disease, but also other age-influenced problems, such as renal [kidney] disease, tumours [cancer] and possibly bone problems, like osteoporosis.

HTU: In the UK there's concern over increasing heart problems in the

population in general, due to an increase in unhealthy lifestyles. How much do you think this contributes to cardiovascular risk in people with HIV?

MN: We all want to enjoy ourselves but we must be aware of the risks.

Certainly the excessive smoking rates in people with HIV are important.

NP: I think our patients have similar risks as the general population and we should be promoting healthy lifestyles for everyone. However, we know that some patient groups are going to be more at risk and I think that people with HIV should be included alongside patients with diabetes or heart problems, when it comes to having routine health screens. Also, our patients have the same risk factors, like smoking and family history, but being on antiretrovirals may add to those risks.

HTU: What recommendations would you make to patients in terms of beneficial lifestyle changes?

MN: The same as to any individual: DON'T smoke; drink alcohol in moderation; maintain a good diet; and get plenty of exercise. However, we all have to live. In some ways combination antiretrovirals have given individuals a



beating heart disease

The following links may be useful if you're considering lifestyle changes to reduce your risk of cardiovascular disease:

www.nhs.uk/gosmokefree - for advice on quitting smoking

www.nhs.uk/conditions/cholesterol - nutritional advice to lower cholesterol

www.gmfa.org.uk - GMFA run quit smoking courses specifically designed for gay men

www.aidsmap.com - NAM fact sheets and booklets on nutrition and exercise

second life so people should enjoy the benefits – but it's about moderation.

NP: Advice depends on the individual patient. We would encourage all patients who smoke to stop and we would encourage them to see the smoking cessation nurse from the hospital or via their GPs. Exercise doesn't have to be a full-on gym workout – walk instead of getting on the bus or get off a few stops earlier, take the stairs instead of a lift. If patients have raised lipids (levels of fat in the blood) then I would advise on a healthy diet. I ask them to keep a food diary for a week to see exactly what they are eating and refer them to a dietician if necessary. But any nurse can advise on eating more fruit and vegetables, lean meat like chicken and fish, etc. There are drinks like *Benecol* that can also help to reduce cholesterol.

HTU: Studies have suggested that treatment with either protease inhibitors or, more recently, abacavir and didanosine (ddi) can boost the risk of heart disease. What's your advice to people taking these drugs and are some people at greater risk?

MN: Data from the D:A:D study would suggest an independent risk from PIs and the NRTIs abacavir and ddi. However, this was a cohort study rather than clinical trial. It's important to remember that cohorts can only suggest and do not prove. No one should panic and don't just stop the drugs. Talk to your doctor if you are concerned, as there are probably alternatives. The risk is negligible when compared with the benefits of antiretrovirals and the data on abacavir would suggest a risk equivalent to that of smoking. So if you smoke, stop. In my practice, some

individuals have chosen to swap drugs if they have a good and simple alternative and some have chosen to remain on their therapy.

HTU: Do you think lifestyle or choice of antiretroviral drugs plays the most important role in maintaining cardiovascular health?

MN: Lifestyle. We must choose the right drugs for the right patient. In patients with high risk factors, we should try and keep away from drugs that could potentially add to that risk.

HTU: What should patients look for if they think they may be at risk of cardiovascular disease? Are there any tell-tale signs or is it something that is monitored through regular clinic visits?

MN: It is important to have cholesterol checks performed in clinic, as well as regular blood pressure checks and counselling regarding risk factors [such as dietary counselling]. There's also a simple equation, called the Framingham equation, which can tell you your risk, but it's not absolute. Often there are no signs prior to a heart attack, but any chest pain on exertion should be reported.

NP: All patients should have a baseline assessment of their risk of cardiovascular disease at their clinic, especially before they commence antiretroviral therapy. This will consist of height, weight, body-mass index (some data supports using waist measurements to determine whether someone is overweight), blood pressure and lipids (the amount of fat in the blood) – preferably after fasting, but if they haven't fasted they can come back [for a second blood test] if the results are abnormal.

Fasting bloods are better for detecting whether there are problems. Patients will be asked if their mother, father or sibling have had a heart attack or any other major heart problems. All this information can help work out their risk of a cardiovascular event in the future.

HTU: Is there an argument for more cardiovascular disease awareness amongst both HIV specialists and GPs? What role do nurses play?

MN: There is always a need for better education and awareness. HIV physicians are aware that cardiovascular disease is an important part of their role, but, remember, they aren't experts.

NP: Nurses play a key role. In many therapy areas patients may only see a nurse to assess risks, for ongoing monitoring and to provide advice. When time is short with the doctor during the clinic appointment, nurses should have more time to undertake the appropriate tests and to give general advice. If we could get more patients to access their GPs, then practice nurses have even more knowledge and experience about maintaining health. The principles are the same whether you have HIV or not.



news in brief

anti-hiv drugs

Abacavir allergy test works equally well in black and white patients

The HLA-B*5701 genetic test, used to predict who will develop a severe allergic reaction to the anti-HIV drug abacavir, is equally accurate in both black and white people, according to a study published in the April 1st edition of *Clinical Infectious Diseases*.

Every patient, both black and white, with a hypersensitivity reaction to abacavir (confirmed by skin-patch testing) had a positive HLA-B*5701 genetic test in this study. There had previously been concerns that the test was less accurate in black individuals.

Abacavir (*Ziagen*, also in the combination pills *Kivexa* and *Trizivir*) is a potent antiretroviral drug, but a hypersensitivity reaction occurs in between 5% and 8% of those treated with the drug. Allergy to abacavir is strongly associated with the presence of the HLA-B*5701 gene and a test has been developed to monitor patients for its presence. It occurs with greater frequency in patients of northern European racial origin from and is rare in patients of African ethnicity. Earlier research also suggests that the HLA-B*5701 test may be less accurate in black patients than white individuals.

This retrospective US study found that all of the patients, black and white, with a positive skin-patch test – an immunologically confirmed hypersensitivity reaction – had a positive HLA-B*5701 test.

The authors conclude: "these findings support the generalizability of HLA-B*5701 screening for the prevention of abacavir hypersensitivity reactions in US white and black populations."



hiv & mental health

Stress management beneficial for those with HIV

Anxiety, depression and psychological distress are common among people with HIV who are taking antiretroviral therapy, according to a study published in the March 30th edition of *AIDS*. But the trial suggests that a few months of weekly cognitive-behavioural stress management (CBSM) can improve mental and physical well-being.

Psychosocial factors, such as depression, stress, or a lack of social support, are known to influence the course of HIV infection. Such factors can affect the working of the immune system and impact on adherence to anti-HIV treatment.

While trials have looked at outcomes following cognitive-behavioural stress management before, most were conducted before potent anti-HIV treatment became available.

While no differences were seen in the CD4 cell count, viral load or adherence of those receiving the CBSM therapy, when compared to controls, significant benefits were reported in quality of life.

The authors suggest that screening for psychological distress should become part of routine HIV management.

UK policy

Draft BHIVA guidelines recommend earlier start

Starting anti-HIV treatment should be discussed with all patients with a CD4 cell count of around 350 cells/mm³, and therapy should be started as soon as the patient is ready, according to new draft British HIV Association (BHIVA) treatment guidelines.

US and European guidelines have already recommended that anti-HIV treatment should be started when a patient's CD4 cell count is in the region of 350 cells/mm³, because of evidence of an increased risk of HIV-related illness and other serious conditions in those started on treatment at lower CD4 levels. The new UK guidelines raise the threshold for the initiation of treatment from 200 CD4 cells/mm³.

The draft guidelines also recommend efavirenz (*Sustiva*) with *Truvada* (tenofovir and FTC) as the preferred first-line therapy. Abacavir with 3TC has been moved to an alternative choice of regimen. Prof Brian Gazzard, chair of the guidelines committee, explained to a NAM information forum in London that the change for abacavir/3TC occurred because *Truvada* may have a greater effect at reducing a very high viral load. Abacavir with 3TC remains an equal first choice for people starting HIV treatment in the US.

These revised adult treatment guidelines are open for comment until May 16 via the BHIVA website – www.bhiva.org

news in brief

clinical trials

Couples desperately needed for vaccine research

There have been rare occasions where people who have had some exposure to HIV seem to be protected from infection, and scientists are trying to determine if this is linked to some natural ability to fight the virus.

A current study at King's College Hospital will contribute to a global research programme, which they hope will lead to the development of an effective HIV vaccine. But in order to carry out the research, study participants and controls are needed.

HIV-negative couples

HIV-negative couples are needed as controls in the study. You may be able to participate in this important study if you and your partner can answer yes to the following questions:

1. Are you in a relationship where both of you are HIV-negative?
2. Have you been in this relationship for at least 10 months?

3. Are you and your partner both willing to take part in this study?
4. Are you both willing to give blood and urine samples?

Serodiscordant couples

If you are in a relationship where one of you is HIV-positive and the other is either HIV-negative or untested, and you can answer yes to questions 2-4 above, you too could be participants in the study.

If you think you are eligible for this study and would like to find out more, please contact King's College Hospital on Freephone 0800 358 0889, email on

info-chavi@kch.nhs.uk or visit the website at www.kch.nhs.uk/chavi

Enquiries will be treated in strict confidence and you will be reimbursed for your time and travel.



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CPS guidance on criminal prosecution

by Rob Dawson, with extracts from an aidsmap article by Edwin J. Bernard

Prosecutions for HIV transmission have stirred up a great deal of confusion due to a lack of understanding of scientific evidence and of the legal meanings of 'harm' and 'transmission'. With new guidance from the Crown Prosecution Service (CPS) being less than specific, it remains doubtful whether such a complex area will ever have law that is clearly defined.

To date, 13 people in England and Wales have been prosecuted for 'recklessly' transmitting HIV to their sexual partners. All of these cases were brought under Section 20 of the Offences Against the Person Act which came into law in 1861 and so was not designed to deal with cases of HIV transmission. As a result, the law has been cloudy, undefined and open to interpretation.

The CPS issued a first draft of its policy statement on unlawful HIV transmission in September 2006, but, following widespread criticism, it went back to the drawing board. After a long consultation process with HIV organisations and the general public, new guidelines have now been released for prosecutions involving the

intentional or reckless transmission of sexually transmitted infections. The guidelines outline offences that would be considered 'intentional' or 'reckless', clarify what needs to be proven in order for charges to be brought, and discuss witness and victim care issues.

Although the policy statement and legal guidance have been welcomed by some major HIV policy organisations, because of the clarifications they offer, some legal experts say the documents are vague. The CPS documents deliberately avoid referring to a particular sexually transmitted infection, keeping their advice generic. Neither HIV nor condoms are specifically mentioned, despite the fact that all prosecutions in England and Wales have been for reckless HIV transmission, and important questions remain unanswered.

What is clarified?

Two national HIV policy organisations, Terrence Higgins Trust (THT) and the National AIDS Trust (NAT), have already published documents providing initial, brief summaries of the CPS policy (web links to these can be found below).

In short, the policy clarifies that:

- Prosecutions are unlikely to take place as a result of one-off sexual encounters. The legal guidance for prosecutors says: "It will be highly unlikely that the prosecution will be able to demonstrate the required degree of recklessness in factual circumstances other than a sustained course of conduct during which the defendant ignores current scientific advice regarding the need for and the use of safeguards."
- Scientific evidence must be used to show that the defendant infected the complainant. Even if someone

is thinking of pleading guilty, scientific evidence must show that they are likely to be the source of infection. Phylogenetic analysis (genetic analysis to find similarities between the strains of HIV in two different individuals) can be used, but this alone is not conclusive proof. Enquiries will have to be made about the sexual behaviour and sexual history of the complainant to ensure that the infection could not have come from an alternative source.

- The defendant has to have known they were infected when transmission took place in order to be convicted. This usually means that they should have a formal diagnosis, but there are other rare circumstances (e.g. where someone has very good reason to believe they are infected but refuses to be tested) that could result in prosecution and conviction.
- In order to be convicted, the CPS must prove that the defendant understood both that they were infectious to other people and how the particular infection is transmitted.
- Informed consent to the risk of HIV infection is a defence against a charge of reckless HIV transmission. This means that the HIV-positive partner will need to show that they disclosed their status before consensual sex. The CPS will also allow for other possible ways in which the complainant might have been 'informed' of the defendant's HIV status – whether from a third party, or a hospital visit, or from obvious symptoms of infection.
- Consistent, correct condom use is a defence against a charge of reckless HIV transmission. However, the



CPS doesn't use the word 'condoms' because it appears to be trying to cover a wide range of differently transmissible conditions. The word 'safeguards' is used throughout the guidance, which suggests that condoms and other safer sex techniques, used in good faith, would constitute a defence. Essentially, there would have to be proof that such 'safeguards' were absent, inappropriate or inadequate for prosecution to occur. However, this may be subject to interpretation by expert witnesses.

- Transmission must take place for a recklessness charge. There is no crime of 'attempted reckless transmission'. THT says it has "seen a number of cases where local CPS officers have tried to bring non-existent charges, mainly of attempted recklessness." They add: "It is very helpful that the CPS have stated clearly that this is not appropriate. However, it is possible to bring a charge of attempted intentional transmission." To date, nobody has been successfully prosecuted for intentional transmission.

Prosecution difficult

Prosecutions for reckless or intentional transmission of HIV are likely to remain difficult and complex. Lack of evidence in three English prosecutions for HIV transmission has already resulted in the defendant being cleared.

The CPS policy document says in its conclusion that "cases involving the intentional or reckless sexual transmission of infection may raise very difficult and highly sensitive issues. We recognise that obtaining sufficient evidence to prove the intentional or reckless sexual

transmission of infection will be difficult and that accordingly it is unlikely that there will be many prosecutions."

NAT's Chief Executive, Deborah Jack, notes that "this new guidance from the CPS is helpful in clarifying the prosecution process. The level of evidence needed to prove intentional or reckless sexual transmission of infection has rightly been set very high and it is unlikely that there will be many prosecutions."

Disappointment

While any clarification of the law has been welcomed, NAT admit they are disappointed with some of the guidance. Yusef Azad, NAT's Director of Policy and Campaigns, told **aidsmap** that "there is no definition of what constitutes reckless behaviour in relation to HIV transmission. In some ways this could be a good thing [because] at least we don't have an incorrect or unhelpful definition. But the CPS leave it instead to individual clinicians to advise in each case, with a worrying possibility of inconsistent approaches and clinicians simply rehearsing their own ethical opinions, rather than providing objective expert advice."

It should also be noted that the CPS only become involved once a case has been investigated by the police and that so far there is no guidance for the police in this area.

Some questions still remain and the law can be unclear. The guidance cannot take the place of appropriate legal advice, and anyone personally concerned about the possibility of prosecution should contact THT Direct as soon as possible on 0845 1221 200 to be put in contact with expert legal advisers. ■

further information

Policy for prosecuting cases involving the intentional or reckless sexual transmission of infection: www.cps.gov.uk/publications/prosecution/sti.html

Legal guidance for intentional or reckless sexual transmission of infection: www.cps.gov.uk/legal/section7/chapter_h.html

Summary of the policy from THT: www.tht.org.uk/binarylibrary/cpsupdate.pdf

Summary of the policy from NAT: www.nat.org.uk/document/419

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