

aids treatment update

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in this issue

Those of us taking anti-HIV drugs on a daily basis – not to mention all the other pills and potions we ingest – are putting our livers under quite a lot of strain. Fortunately, the liver is an amazing organ, sorting out and cleansing everything we put into our bodies, and it rarely seriously malfunctions. But if the liver is also infected with hepatitis viruses B or C, this becomes more of an uphill battle.

Serious liver-related problems can occur without being infected with these viruses but being coinfecting with hepatitis viruses greatly increases the chances of becoming sick; not from HIV, but from hepatitis.

Treatments are getting better, but they're not easy to tolerate, especially for hepatitis C. Fortunately, there's a vaccine against hepatitis B and you should find out if you're already protected, and if not, get vaccinated, even if your HIV doctor never mentions it.

However, there's no vaccine against hepatitis C, and as well as being transmitted via blood, there's a risk that this virus can be passed during sex between HIV-positive people (definitely between men, but possibly also between men and women). Consider this important information when you are deciding whether or not to use condoms with a partner of the same HIV status.

page 3 In *upfront*, Edwin J Bernard examines the future of treatment interruptions in the wake of the SMART study being discontinued early.

page 4 In *The ABCs of liver disease*, HIV and hepatitis experts, Dr Mark Nelson from London's Chelsea & Westminster Hospital, and Brighton and Sussex University Hospital's Dr Martin Fisher, explain to Edwin J Bernard why preventing and treating hepatitis B or hepatitis C isn't so simple in people coinfecting with HIV.

page 8 In *Accidental Damage*, Gus Cairns explains how some drugs can damage the liver as badly as viral hepatitis, and how to avoid drug-induced liver injury. Plus, a guide to liver function tests.

page 12 Amongst the items in *News in Brief*, we discover cautious excitement over a brand new class of drugs, integrase inhibitors, balanced with more evidence confirming the side-effects of currently approved anti-HIV therapy.

page 14 An easy alternative to liver biopsies might be just around the corner thanks to an exciting – and expensive – piece of new technology called *FibroScan*, according to Dr Sanjay Bhagani of London's Royal Free Hospital, and the Chelsea & Westminster's Dr Mark Nelson.



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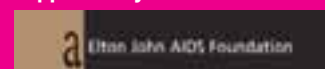
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not so smart?

is there a future for treatment interruptions? by Edwin J Bernard

When it was announced in January that the SMART (Strategies for Management of Antiretroviral Therapy) study was stopped early due to more than twice as many participants taking treatment interruptions getting sick or dying compared with those on continuous treatment, it was assumed by many that this now means anti-HIV treatment is for life.

SMART was the world's largest trial designed to compare episodic use of anti-HIV treatment based on CD4 cell count against continuous anti-HIV therapy. It was supposed to last for up to nine years and answer many important questions, although the main one was: Can people who take treatment breaks that never allow their CD4 cell counts to drop below 250 cells/mm³ stay as well as people who take continuous anti-HIV therapy?

When we last reported on the study (ATU 138) one of our main concerns was that people who had previously had very low CD4 cell counts (below 200 cells/mm³) were being allowed into the study, even though other, small studies had found that treatment interruptions were more likely to be dangerous for them.

One of the biggest surprises of the SMART study results presented last month in Denver at the most important scientific HIV meeting of the year, the Conference on Retroviruses and Opportunistic Infections (CROI), was that it failed to detect a link between

the risk of disease progression and the lowest-ever CD4 cell count.

Instead, they found that viral load at the start of the study was linked to an increased risk of disease progression. Although there was no difference in risk among those entering the trial with viral loads above 400 copies/ml, people taking treatment interruptions who had a viral load below 400 copies/ml before they stopped treatment had a risk of progression almost four times greater than those on continuous therapy.

An even bigger surprise was the study's findings that the participants who interrupted their therapy were one-and-a-half times more likely to experience the kinds of serious complications that scientists had always thought were anti-HIV drug side-effects. These included heart attack, stroke, and kidney or liver disease.

Dr Wafaa El-Sadr, who presented the SMART data at CROI^[1], suggested that increased levels of inflammation, possibly due to the longer amount of time spent at lower CD4 cell counts (or at higher HIV levels) in the treatment interruption group, could be responsible for the increased incidence of these serious complications. Although some experts agree with her, this is only speculation. If this does turn out to be the case, however, it may force us to reassess the issue of anti-HIV drugs' side-effects: what is HIV-related and what is drug-related?

Interestingly, another treatment interruption study that presented results

at CROI, Staccato^[2] - which kept CD4 cell counts higher throughout the study by restarting therapy when CD4 cell counts fell below 350 cells/mm³ - did not find an increased risk of disease or complications in those who interrupted their therapy. However, this was a much smaller study, and direct comparisons cannot be made.

Other experimental strategies, including treatment simplification, still offer the hope of reduced pills and fewer side-effects, and some clinical trials that include treatment interruptions are continuing in order to see whether stopping anti-HIV therapy is possible using therapeutic vaccines.

Although the SMART results provide strong evidence that CD4-guided treatment interruptions are risky in treatment-experienced patients who previously had good control of HIV, people with HIV are always going to need, or want, to interrupt therapy. For now, however, interrupting treatment should be thought of as a harm-reduction necessity rather than an HIV treatment strategy.

If you are currently on a treatment break - either as part of the SMART study, or in consultation with your HIV doctor - you should talk to your doctor as soon as possible about the pros and cons of going back on treatment. ■

the ABCs of liver disease

why preventing and treating viral hepatitis isn't as simple as ABC, by Edwin J Bernard



Summary

- Anyone with HIV can also be infected with hepatitis A, B or C.
- Hepatitis A is unpleasant, but not serious, and there's a vaccine.
- If left untreated, hepatitis B and C can cause serious liver disease.
- Everyone with HIV should make sure they are vaccinated against hepatitis B.
- Safer injecting and safer sex is the only way to protect against hepatitis C.
- Hepatitis B treatments have improved greatly in the past few years.
- Hepatitis C treatments are harder to tolerate, but can be successful with the right support.

“the risk of acquiring hepatitis C depends on the number of sexual partners and the type of sex you have”

Over the past few years it has become clear that large and previously hidden epidemics of hepatitis B and C infection have emerged among some groups of people already affected by HIV. People who share needles to inject drugs are most likely to be affected, although anyone with HIV can also be coinfecting with hepatitis A, B or C.

Whilst vaccines exist to protect people from hepatitis A and B, there is no vaccine against one of the most serious of viral hepatitis infections, hepatitis C. In the UK there is currently an outbreak of recent (acute) hepatitis C infection, primarily affecting HIV-positive gay men in London and Brighton. But sexually transmitted HCV can also occur heterosexually: a recent French study^[1] concluded that two HIV-positive women out of a group of 402 recently-infected people probably acquired HCV through vaginal sex. The risk, however, depends on how likely your partner is to have HCV: partners of injecting drug users would be at most risk.

Although hepatitis A is an unpleasant short-term illness, it is not associated with long-term harm to the liver. However, hepatitis B and C infections can lead to serious liver disease, and as people with HIV live longer due to the success of anti-HIV therapy, we are now seeing proportionally more liver disease due to hepatitis coinfections than ten years ago.

Complicating matters is the fact that, over time, many drugs used to treat HIV have the potential to harm the

livers of people coinfecting with chronic viral hepatitis. A recent study from the 11,000-strong EuroSIDA cohort^[2] which examined deaths from liver-related causes in people with HIV throughout Europe, found that although the overall death rate from liver-related disease fell after the introduction of potent anti-HIV treatment, coinfection with hepatitis B virus and/or hepatitis C virus and length of exposure to anti-HIV therapy were found to be significantly associated with an increased rate of liver-related death. “This may be due to longer survival in coinfecting patients,” suggested the EuroSIDA investigators, “or prolonged treatment with potentially hepato[liver]toxic drugs.”

That’s the conundrum of hepatitis and HIV coinfection: the anti-HIV drugs keeping coinfecting people alive longer may also be responsible for their ultimate demise. “Fortunately, we are finally taking hepatitis coinfection seriously,” says Dr Mark Nelson, director of HIV services at London’s Chelsea and Westminster Hospital, and one of the organisers of the Second International Workshop on HIV and Hepatitis Coinfection, held in Amsterdam in January. “Before highly active antiretroviral therapy (HAART) came along ten years ago, we used to tell coinfecting patients, ‘Don’t worry, you’re going to die from your HIV’. Then everyone got so excited about HAART they forgot about hepatitis, and that may have been the reason for the recent spate

of studies that found coinfecting people continued to die faster.”

We already have better treatments for hepatitis B, and whilst hepatitis C treatments are becoming more effective, they still require coinfecting individuals to put their lives on hold for a year or so. There is still much to learn about the ideal time to start and stop anti-hepatitis therapy. Dr Martin Fisher, HIV consultant at Brighton and Sussex University Hospitals, where around 8% of HIV patients are coinfecting with hepatitis B and another 8% with hepatitis C, acknowledges that even the ‘experts’ don’t know everything. “Finally, though, some good prospective studies are starting to address some of the key questions we have about treating hepatitis B and C in coinfecting individuals,” he says.

At long last, with the establishment of coinfection clinics at some HIV treatment centres, the development of the British HIV Association’s (BHIVA’s) coinfection guidelines, national and international coinfection meetings, and the recent establishment of the British Coinfection Association, HIV medicine is finally coming to terms with the seriousness of viral hepatitis in HIV-positive individuals. “But still it’s a sleeping giant,” warns Dr Nelson, who is diagnosing acute and chronic hepatitis B and C in his HIV patients every week. “As time goes on, unless we treat people with effective and tolerable drugs there is going to be a proportion of people who are going to get sick and die.”

If there's a vaccine for hepatitis B, why are HIV-positive people still getting infected?

Who is at risk for hepatitis C, and what can you do to prevent infection?

It seems we're much further along for treatments for hepatitis B compared with hepatitis C. What have we learned from the recent Amsterdam workshop?



Martin Fisher

HIV care can be so centred around anti-HIV therapy that a lot of the very basic things can get missed, like screening for hepatitis A, B and C, and offering vaccination against both hepatitis A and B. Everybody with HIV should be tested and vaccinated against hepatitis B. If the first vaccination doesn't work, which can happen in people with HIV, it's worth having another go when CD4 cell counts are higher and viral load is undetectable.

Mark Nelson

There's no excuse for someone who is HIV-positive to get acute hepatitis B. It's usually the doctor's or nurse's fault, though, because everyone who is HIV-positive should be vaccinated. I think it's important that all doctors and nurses are aware of the importance of hepatitis B vaccination, and that patients are aware that once they start a course of hepatitis B vaccinations they should finish it.

Mark Nelson

The major route of transmission is through either transfusion of blood products or sharing of needles associated with injecting drug use. But right now there is an outbreak of acute hepatitis C that is being spread sexually, mainly in gay men with HIV. We don't really know what's going on in the GU clinic or in the general heterosexual population, because you don't usually become sick from hepatitis C when you catch it, and we're diagnosing this as part of the standard of HIV care. When we do liver function tests, if they're abnormal, we then test for hepatitis C.

Martin Fisher

Certainly, data coming from Brighton as well as London's Royal Free and Chelsea & Westminster Hospitals suggests that your chance of acquiring hepatitis C is related to both your number of sexual partners and also to the type of sex you have.

Mark Nelson

We're finding that the gay HIV-positive men who are being diagnosed with hepatitis C are much more likely to have visited sex clubs, bathhouses, saunas; much more likely to have met their partners on sex internet sites; and have much higher rates of partners compared with gay HIV-positive men who don't have hepatitis C. They're also more likely to have insertive and receptive anal intercourse, and practice rimming and fisting - both receptive and insertive - and use sex toys.

Martin Fisher

It's possibly related to recreational drug use, as well. So it may not just be the sex by itself but also the environment in which the sex is occurring. Clearly, some drugs may disinhibit sexual behaviour, whereas sharing 'straws' when snorting cocaine, for example, has the risk of contaminated blood spreading from one person to another.

Mark Nelson

I think we're lucky in that we can treat HIV and hepatitis B with the same drugs: 3TC (lamivudine/*Epivir/Zeffix*) is already approved for both, and data on tenofovir (*Viread*) is looking great. The key messages from Amsterdam were: don't use 3TC against hepatitis B on its own because of resistance; tenofovir - although not licensed for hepatitis B - is probably better than its brother drug adefovir (*Hepsera*); and you may as well give tenofovir and 3TC (or with FTC in the single pill, *Truvada*) together, since you're not going to lose anything because that's the 'gold standard' for HIV.

Martin Fisher

And if you don't need to treat the HIV then you'd need to use agents that are only active against hepatitis B [like entecavir (*Baraclude*), adefovir or interferon] since just using one or two drugs that are also active against HIV, like 3TC or tenofovir, would potentially lead to HIV drug resistance.

Are experts now agreed on when to treat acute hepatitis C?

Martin Fisher

There wasn't any clear consensus from Amsterdam whether you should just get on and treat, or whether you should wait twelve weeks to see if you clear the virus spontaneously - which is what we've tended to do in the UK.

Mark Nelson

There's never a consensus about anything! One-in-four people can clear this virus spontaneously, within about twelve weeks from infection. But while you're waiting you need to check hepatitis C viral load every four weeks. If it's going down, fine, I think you can wait twelve weeks. If not, then I think treatment makes sense. But there are some data in HIV-negative individuals that suggests treatment may not be as successful if you wait, so you have to balance the pros and cons. I leave it up to the patient. I think most would prefer to take the risk of the hepatitis C actually going away by itself rather than taking interferon straight away.

Treating hepatitis C is much more challenging than HIV, particularly when it comes to side-effects like depression and fatigue. How do you support people?

Mark Nelson

I think it's the *idea* of treatment that is actually more frightening than the reality. The treatment works - especially for acute hepatitis C - and it can be lifesaving for those people who are chronically infected. Yes, it's fairly toxic; yes, it can make you feel flu-like symptoms; yes, it can make you depressed; but I find that with the right support - including antidepressants and sleeping tablets - most people can tolerate the treatment very well.

Martin Fisher

Here in Brighton - and I think most coinfection clinics in the UK are the same - we have clinical nurse specialists who support patients taking treatment on an ongoing basis. There's usually a lot of input with anti-HIV therapy at the beginning, and then things tend to sort themselves out and become easier, whereas with hepatitis C therapy the problems usually last throughout treatment, or may even get worse. So that input needs to be regular and ongoing. A lot of it is really acknowledging that people are having a really rough time, and then reassuring them that that's normal.

Hepatitis C therapy does seem to be in the Dark Ages, especially compared with HIV therapy. When will the Age of Enlightenment arrive?

Mark Nelson

HIV and hepatitis C were really discovered around the same time, so there does seem to be a huge contrast when you compare them: why are there no oral drugs for hepatitis C yet? There are some on the horizon [Schering-Plough's hepatitis C protease inhibitor SCH 503034 has just been fast-tracked by the United States' Food and Drug Administration (FDA), and Vertex Pharmaceuticals hepatitis C protease inhibitor, VX-950, is in Phase II studies] but the disappointing thing about them is that, in the studies so far, they're just an add-on to the interferon, not a replacement. In addition, something that came up repeatedly at the Amsterdam workshop is that people with HIV are excluded from the majority of these studies. So, even if they are approved, we'll have to wait while more studies are done in coinfecting individuals. I think it's really important that doctors, patients and advocates lobby the drug companies to get at least some data now in HIV-positive individuals, so that we can all benefit from the new drugs at the same time. ■



Summary

- Many drugs can damage the liver, including anti-HIV medicines and recreational drugs.
- However, over-the-counter paracetamol is the most common liver-damaging drug.
- Liver damage is more likely if you have a pre-existing liver problem, like viral hepatitis, or drink a lot of alcohol.
- Having regular liver function tests will help ensure any problems are dealt with promptly.

Hepatitis - inflammation and damage to the liver - isn't only caused by viruses. Chemical hepatitis, or drug-induced liver injury, is the most frequent cause of acute (as opposed to gradual) liver failure, exceeding all other causes combined. It is also the most common reason experimental drugs fail to reach the market, as was the case with the recent experimental CCR5 inhibitor, aplaviroc.

Although mild disturbances in the way the liver functions are very common when we start taking a new drug (or a combination of new drugs), it usually takes an unfortunate chain of events for these drugs to cause serious liver injury or death: a drug (or a combination of drugs) that is prone to cause liver damage; missed appointments and/or poor monitoring; and often existing, but perhaps undiscovered, liver damage coupled with excessive alcohol consumption.



accidental

why it's good policy to ensure that drug-induced liver injury doesn't happen to you, by Gus Cairns

All about the liver

The liver is an immensely resilient organ. It has to be: every foreign substance taken in by the body is processed by the liver, which is the body's chemical processing plant, energy stockpile and recycling station.

It is the only major organ that will regenerate from a bit of itself, and usually has a big enough reserve of surplus liver cells (called hepatocytes) to deal with the toughest reprocessing job. It takes old red blood cells that have passed their sell-by date, extracts the iron-containing pigment, and in a piece of biochemical thriftiness, makes a bitter green fluid called bile out of them which is used to digest fatty foods. It stores energy in the form of glycogen - a form of glucose.

And its cells contain several hundred different enzymes from the cytochrome P450 family. Each of these has expertise in transforming a particular class of drugs into substances that can be more easily eradicated by the body - usually by chopping or adding bits that make them more soluble in water.

And that, generally, is where the trouble lies. Some drugs are processed nice and tidily and get excreted without fuss. But in others, the soluble

liver product (called a metabolite) is more toxic than the original drug itself.

The best-known example is alcohol, where a different enzyme called alcohol dehydrogenase turns it into the more soluble but much more poisonous chemical acetaldehyde. In the short-term, the result is a hangover, but long-term (chronic) alcohol abuse can lead to fibrosis and cirrhosis.

Fibrosis and cirrhosis

A number of chronic conditions can eat away at the liver's reserve: chronic hepatitis B and C, alcohol and drug abuse, and even an autoimmune condition in which the body's own defences attack the liver can destroy liver cells. These turn into scar tissue (fibrosis) and eventually the whole liver can become hard and inelastic, its channels blocked and its processing capability down to a fraction of what it should be (cirrhosis).

"Fibrosis does not in itself make it more likely you will get liver damage from a drug," explains Dr Gary Brook, Head of Department in GU and HIV Medicine at northwest London's Central Middlesex Hospital, and co-author of several British HIV Association's (BHIVA) guidelines on hepatitis co-infections and liver

transplantation. "But if you already have fibrosis you have less spare capacity. For example, although nevirapine is the anti-HIV drug most often associated with liver damage, even efavirenz (*Sustiva*), the other non-nucleoside, can cause severe liver damage in about 3% of patients. If you already have some fibrosis, however, this risk rises to about 8%. In our experience, being coinfecting with chronic viral hepatitis B or C - the main cause of fibrosis in people with HIV - can double or triple the risk of drug-induced liver injury."

Other factors, and alcohol in particular, can tip the balance decisively. "Even in patients with quite severe liver damage," says Dr Brook, "paracetamol is safe as long as you don't overdose. But in someone who drinks a lot, an 'overdose' might only be twelve 500mg tablets a day; 50% more than the recommended maximum dose." This can happen, for example, if you are combining paracetamol with other cold remedies that also contain the drug.

Which drugs can damage the liver?

All drugs have the potential to hurt the liver, including many used by HIV-positive people, but there are no definitive data that can provide a



damage

pecking order of drug-induced liver injury, not even in a group of patients as intensively-studied as those living with HIV.

"Our figures come mainly from drug trials," says Dr Brook. "Unfortunately no-one has done large enough studies to pick out which drugs cause the most problems in the real world."

To help remedy this situation, in 2004 the United States National Institute of Health (NIH) began a three-year study of patients who suffer severe liver injury due to both prescription and over-the-counter medications, but results aren't yet available. And in Europe, the body responsible for licensing new drugs, the European Medicines Evaluation Agency (EMA), is now monitoring liver toxicity in HIV-positive people based on the model of one that already exists on lipodystrophy.

They have expanded the D:A:D (Data collection on adverse events of anti-HIV drugs) study - which currently monitors the frequency of heart attacks and strokes in people on HIV medication - to also look at drug-induced liver injury. Their preliminary findings, reported at the

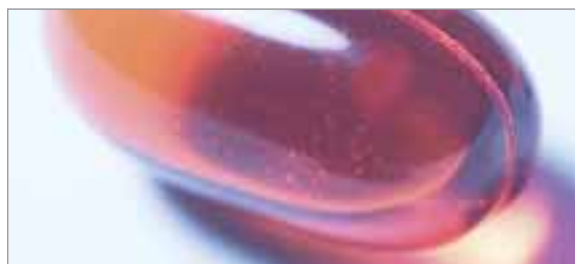
13th Conference on Retroviruses and Opportunistic Infections (CROI) held in Denver last month^[1], suggest some evidence of an increased risk of death due to drug-induced liver injury of 10% per year of anti-HIV therapy once latest CD4 counts had been adjusted for, although the investigators say that a longer study period is required before firm conclusions can be drawn. However, the main risk factors for liver-related death were low CD4 counts, chronic coinfection with hepatitis B and C, and older age.

Currently the only information that helps identify individual drugs associated with serious drug-induced liver injury come from the World Health Organization (WHO) which keeps a database of around 5000 reports of deaths between 1968 to 2003 that appear to be caused by liver-toxic drugs^[2]. "It's a very ad-hoc collection of largely American cases," comments Dr Brook, "but it does give an approximate guide to the most troublesome drugs. What's notable is that four anti-HIV drugs are in the Top Ten and another is a drug used to prevent and treat an AIDS-defining illness."

It's important to remember that this list reflects the popularity of drugs as well as their absolute liver toxicity, which explains the high position on the list of the widely-used 3TC which is relatively less liver-toxic than, say, the less commonly-used nevirapine. Other drugs just outside the Top Ten include the painkiller diclofenac (*Voltarol*), the antibiotic amoxicillin/clavulanate (*Augmentin*), and the anti-tuberculosis (TB) drug isoniazid.

But virtually any drug can cause liver problems in at least a handful of people, and it's not only prescribed drugs that can cause drug-induced liver injury. Top of the list - and accounting for 30% of all cases reported to the WHO - is the over-the-counter painkiller and fever-reducer, paracetamol, which is also found in all kinds of cold remedies.

Recreational drugs can also cause liver injury. "When I was working in A&E," recalls BHIVA hepatitis guidelines co-author, Dr Janice Main, who is a consultant in infectious diseases and general medicine at Imperial College School of Medicine at St Mary's Hospital, London, "we used to talk about 'hepatitis E'. This doesn't refer to a rare viral type, but to the liver



WHO's top ten liver-toxic drugs

1 Paracetamol/acetaminophen
(painkiller)

2

Troglitazone
(anti-diabetes, now discontinued)

3 Valproic acid
(anti-epilepsy; also being used as an experimental immune modulator in HIV)

4

Stavudine/d4T/*Zerit*
(anti-HIV)

5

Halothane
(anaesthetic, now discontinued)

damage we'd see that was caused by ecstasy every weekend. Cocaine overdoses can damage the liver, too."

Even complementary therapies can be liver-toxic. Dr Main has seen liver failure due to the herb butterbur, used to treat hayfever and sinusitis. Herbs that have been banned in various countries due to their potentially liver-damaging properties include the tranquillising herb, kava-kava, and the Chinese herb ma huang, also known as ephedra.

How do you know if your liver is sick?

In general, doctors rely on a battery of blood tests to pick up on what's happening in the body. These detect a variety of chemicals that are markers of liver damage. They include the following:

- Waste products the liver is failing to clear

The most important of these is bilirubin, the waste from old red blood cells. The yellowing appearance of jaundice, caused by an excess of bilirubin in the blood and tissues, is the surest sign that liver damage is severe and the drug needs to be stopped. "Jaundice is a key feature of predicting how severe

liver damage is," says Dr Brook. "The liver failure rate among patients with acute liver injury who have jaundice is about 11%."

- Chemicals found in the liver that shouldn't be in the blood

These are the liver enzymes, which should normally sit inside cells doing their processing jobs, but which spill out when liver cells rupture and die. The most important one is ALT (alanine aminotransferase). This is an enzyme whose abnormal presence in the blood signals the rupture of liver cells. Normal levels are less than 40 IUs (international units) per litre. Over 200 IU suggests liver problems, but, says Dr Main, "we get really worried if it's in the thousands."
- Chemicals the liver should be making, and isn't

The most important one of these is the protein albumin, a substance made in large quantities by the liver that regulates the body's fluid balance. "Albumin acts like a sponge," explains Dr Main. "If there's not enough of it, you get ascites." Ascites (pronounced a-site-ease) is the accumulation of

fluid in the belly that is a sign of end-stage liver failure, and usually means a liver transplant is necessary. At this point the liver has come to the end of its reserves and has given up doing the most basic biochemical jobs (known as 'decompensation').

However, there's usually plenty of time to remedy the situation before you begin to have symptoms of liver failure, which tend to occur in a specific sequence. "The first thing people often notice is severe loss of appetite, often with nausea," says Dr Main. "If you're a smoker, you go off cigarettes too! Then you may notice you feel very fatigued and weak. Sometimes you get very itchy or may need to drink a lot of water. You may also notice yourself bruising easily - this is because the liver makes the factors that make blood clot. Light-coloured stools and dark urine usually herald the appearance of frank jaundice, often noticed first in the whites of the eyes."

"Eventually you would start to get fluid accumulation in the belly," Dr Main adds, "but by this time you hopefully will have gone to hospital." ■



6 Lamivudine/3TC/Epivir/Zeffix
(anti-HIV, anti-hepatitis B)

10 Cotrimoxazole/Septin/Bactrim
(antibiotic, used to prevent and treat Pneumocystis pneumonia/PCP)

8 Amiodarone/CordaroneX/Amyben
(heart disease)

7 Didanosine/ddI/Videx/Videx EC
(anti-HIV)

9 Nevirapine/Viramune
(anti-HIV)

news in brief

new drugs



Cautious optimism for new class of anti-hiv drugs

Exciting new data from a brand new class of anti-HIV drugs called integrase inhibitors were presented last month in Denver at the Thirteenth Conference on Retroviruses and Opportunistic Infections (CROI). Although there were reports from two integrase inhibitors, Merck's drug, code-named MK-0518, is the furthest along in development, and appears to pack the most potent punch ever seen against HIV that is resistant to most available anti-HIV drugs.

At the moment, the most potent 'salvage' regimen available is the combination of ritonavir-boosted tipranavir (*Aptivus*) with T-20 (enfuvirtide, *Fuzeon*) used with what is known as an 'optimised background regimen' – new and recycled anti-HIV drugs that might still have some effect against HIV, based on the results of resistance testing. Although this combination is helping many highly treatment-experienced individuals stay well, there are some trade-offs: notably, self-injection of T-20 twice daily and the possibility of increased blood fats and liver problems associated with ritonavir and tipranavir, respectively.

Although the MK-0518 data are very preliminary, they compare favourably with the tipranavir/T-20 combo. After 16 weeks on this drug with an 'optimised background regimen', at least 70% of highly treatment-experienced study participants – 98% of whom were resistant to all protease inhibitors – achieved a viral load below 400 copies/ml. Since MK-0518 caused no more side-effects than the participants on an inactive placebo – at least, in the short-term – and it appears not to interact with other anti-HIV drugs, this is a major advance over currently-available therapies. However, MK-0518 is only available in clinical trials: details of UK sites will be announced on aidsmap.com if, and when, phase III studies begin here.

A second integrase inhibitor from Gilead Sciences – code-named GS 9137 – also appears to be very potent in both treatment-naïve and treatment-experienced individuals, according to data from a short-term study presented in Denver. However, this drug needs to be boosted with ritonavir, and is also expected to have some interactions with other anti-HIV drugs.

new drugs



One pill once daily by end of year?

Gilead Sciences and Bristol Myers Squibb (BMS) announced in January that they now have data showing that a fixed dose combination pill combining Gilead's *Truvada* (tenofovir and FTC [emtricitabine]) with BMS's efavirenz (*Sustiva*) provides the same amount of medicine in the blood to fight HIV as the separate components. This once-daily single pill may help people new to anti-HIV therapy adhere better to therapy. The announcement came as a surprise, since the companies had previously announced that they were experiencing difficulties in getting the formulation right. They will be applying for formal US regulatory approval by the middle of 2006; applications for European approval usually lag behind by several months. If approved, the new formulation will be the first once-daily HIV treatment comprising drugs from two classes of antiretrovirals.

new drugs

Another CCR5 inhibitor study terminated

One of several trials of Pfizer's investigational CCR5 inhibitor has been stopped early by the independent Data Safety Monitoring Board (DSMB). A study comparing once-daily maraviroc with efavirenz (*Sustiva*) in over 200 people who had never taken HIV therapy before found that after 16 weeks of treatment, once-daily maraviroc did not prove itself to be "non-inferior" to efavirenz.

latest research



Studies confirm AZT fat loss link, with no easy or fast recovery

Two different studies provide more evidence that AZT (*Retrovir*, and also in *Combivir* and *Trizivir*) is associated with fat loss, or lipoatrophy. One study examined limb fat in two groups of people new to anti-HIV therapy both taking efavirenz (*Sustiva*). After a year, the group that also took tenofovir and FTC (*Truvada*) had significantly more limb fat than those who also took AZT and 3TC (*Combivir*).

Another study found that people who switched from AZT-containing anti-HIV regimens to regimens containing either tenofovir (*Viread*) or abacavir (*Ziagen*) were significantly less likely to recover limb fat after a year compared with those who switched from d4T (stavudine, *Zerit*).

d4T was the first drug to be associated with fat loss. The latest studies suggest that whilst AZT may take longer to cause fat loss than d4T, regaining some of this lost fat after stopping the drug may also take longer.

Switching early from AZT or d4T (or never taking them in the first place) appears to be the best way to avoid fat loss, even though a variety of treatments are being investigated to treat this side-effect.

The most promising so far is the anti-diabetes drug, pioglitazone (*Actos*), which was reported in Denver to increase limb fat by about 400g after a year in people with lipoatrophy who were not taking d4T at the same time. However, since they started with an average of 2.9kg, and the amount of limb fat in the general population is around 8kg, no-one on the drug actually noticed the difference.

the new hiv news update from nam

news from *hiv weekly*

The number of people dying of AIDS has fallen dramatically since effective anti-HIV treatment became available in the mid/late 1990s. However, even in the United Kingdom and other European countries where there is widespread use of anti-HIV drugs people still die of AIDS.

The cancer non-Hodgkin's lymphoma has become a lot more rare in HIV-positive people due to HIV treatment, but it accounts for about a quarter of AIDS cases in countries like the UK. HIV-positive people who develop non-Hodgkin's lymphoma normally have very low CD4 cell counts.

A French study has now found that having a high viral load for a long period may be a risk factor for the development of non-Hodgkin's lymphoma. However, they also found that the risk declined after six months of being on anti-HIV therapy. Unlike other studies, the French doctors did not find that the lowest ever CD4 cell count or CD8 cell count were risk factors for developing lymphoma.

subscribe to *hiv weekly*

NAM has launched a new, weekly email bulletin, *HIV Weekly*, that provides people affected by HIV with a concise, plain English digest of the very latest HIV news. The bulletin is edited by Michael Carter, NAM's patient information and news editor.

One of the unique benefits of *HIV Weekly* is the inclusion of hyperlinks within the stories so that you can quickly and easily access further information on NAM's website, aidsmap.com, with the click of a mouse. Information and news about the latest NAM treatment information resources will also be included in the bulletin.

To receive your free weekly news digest visit www.aidsmap.com/hivweekly

latest research

PIs, not NNRTIs, increase heart attack risk

The 16% per year increased heart attack risk seen in people taking anti-HIV therapy is caused by protease inhibitors (PIs) and not non-nucleoside reverse transcriptase inhibitors (NNRTIs), according to the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study presented in Denver at the Conference on Retroviruses and Opportunistic Infections. The study showed that this increased risk was partially due to the changes in blood fat levels caused by protease inhibitors.

Fortunately two small and short-term studies are suggesting more effective ways to treat high blood fat levels. The first found that people with high levels of blood fats known as triglycerides but low levels of another kind of blood fats (LDL or 'bad' cholesterol) may benefit from a combination of fish oil supplements and the fat-lowering drug fenofibrate (*Fenogal/Lipantil/Supralip 160*) if they have failed to respond to either treatment alone. The second found that adding the cholesterol absorption inhibitor, ezetimibe (*Ezetrol*), to the fat-lowering drug pravastatin (*Lipostat*) can safely and effectively reduce levels of both total and LDL cholesterol.

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scanning the future

could FibroScan mean the end of liver biopsies? asks Edwin J Bernard

Currently, the most reliable method of judging how damaged the liver has become, due to either hepatitis B, hepatitis C, or drug-induced liver injury, is a liver biopsy. This is the process of extracting a tiny sample of the liver via a needle through the skin, for the purpose of laboratory examination.

Spurred on by patients who are increasingly resisting this unpleasant procedure, some members of the medical community now believe that liver biopsies are unnecessarily invasive, and that there are less traumatic alternatives.

The most promising of these is ultrasound elastography, a French invention with the trade name, *FibroScan*. It is a risk- and pain-free examination with an instantaneous result: an ultrasound probe is simply held against the skin where it detects the degree of stiffness in liver tissue in a process that lasts under than ten minutes.

A recent French study^[1] found that it was efficient in detecting serious liver damage in patients coinfecting with HIV and hepatitis C. However another study, in HIV-negative patients with hepatitis C, found that *FibroScan* alone wasn't as effective in determining light-to-moderate liver damage, and suggested that *FibroScan* in combination with a non-invasive blood test known as *FibroTest* would give the most reliable results^[2].

Since it is a new invention, and has not yet undergone rigorous scrutiny by the National Health Service, the machine, which costs around £40,000, is not yet routinely available in the United Kingdom, although it is already being used in some hospitals in France, Italy and Israel.

However, ATU has learned that a *FibroScan* machine is about to debut at one London hospital, and it is hoped that another will appear at a second London site very soon. We asked Dr Mark Nelson from Chelsea & Westminster Hospital, and Dr Sanjay Bhagani, from the Royal Free Hospital to explain the pros and cons of *FibroScan*, and who might benefit from it.

Why do we need alternatives to liver biopsies?

Sanjay Bhagani

Liver biopsies are the 'gold standard' for assessing liver damage but they're not without their problems. It's an invasive, uncomfortable procedure with some, albeit very minimal, risks. There are also substantial costs associated with them – not only in terms of discomfort and risks for the patient, but also in terms of use of hospital beds. There is also an error rate associated with liver biopsies due to variations in the way liver biopsies can be interpreted.

Mark Nelson

Although there is a risk of – sometimes serious – bleeding afterwards, for the majority of people it's safe, if little uncomfortable, and usually not as bad as the patient expects. I should stress, however, that it is something that people don't want, and would prefer not to have, so it's good to try and look for alternatives.

How did the Royal Free Hospital acquire its FibroScan machine?

Sanjay Bhagani

Over the last year or so we've become increasingly aware of the need to try

and offer the best we can for our patients. Currently, there aren't enough data regarding the use of *FibroScan* in HIV/hepatitis C coinfecting patients, and there are even fewer data on the use of *FibroScan* in patients coinfecting with hepatitis B. So we have acquired our machine for research use through an unrestricted educational grant from Gilead Sciences [who produce several drugs for hepatitis B, and are developing oral drugs for hepatitis C].

What's the situation at the Chelsea & Westminster?

Mark Nelson

We've talked to some of the people who already use *FibroScan* in France and Italy and they tell us it's revolutionised patient care in their clinics. Consequently, I think it's something that we need. So, St Stephen's AIDS Trust [an HIV/AIDS charity based at the Chelsea & Westminster] is almost certainly going to buy a *FibroScan* machine. Why is an HIV charity paying for it rather than the NHS? The problem is that although there are some small studies showing that it appears to work very well, NHS guidelines and protocols mean they won't pay for it right now. Hopefully the studies that are done here and at the Royal Free will help pave the way for NHS acceptance.

Who will benefit from the machine right now?

Sanjay Bhagani

To begin with, only patients taking part in research. We plan to compare *FibroScan* against liver biopsies in patients coinfecting with HIV and hepatitis C, and in particular, hepatitis B. Perhaps the most useful thing we'll

be able to do with *FibroScan* is to follow coinfecting patients more closely – perhaps at half-yearly or annual intervals – rather than at the three-year interval currently recommended with liver biopsies. Data presented at the Retrovirus conference last year³ showed that about 25% of patients coinfecting with HIV and hepatitis C progressed faster than expected over those three years, and we want to see if we can use the *FibroScan* to identify the people who are progressing more rapidly.

Mark Nelson

Whilst there are many questions about how to best use the machine – and we don't have one yet – I feel as a trustee of the St Stephen's AIDS Trust that the charity is there to help all people living with HIV, and not just to help a group of patients who attend the Chelsea & Westminster.

Is this the beginning of the end for liver biopsies?

Mark Nelson

We all want *FibroScan* to work, but we have to be aware that anything can be wrong – including liver biopsies.

However, I'm hoping that this may overcome a major hurdle in managing liver disease.

Sanjay Bhagani

I don't think that *FibroScan* could completely replace liver biopsies. There are some things that only a liver biopsy can tell you: *FibroScan* can't tell you how much inflammation there is in the liver or what's causing the liver damage, or how much steatosis (fatty liver) there is. We still need to work out how best to utilise *FibroScan*, but I suspect it may be most useful in monitoring patients more frequently, as well as monitoring response to treatment.



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Where to find out more about HIV

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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.

■ Information events in London

On the last Monday of every month, an expert speaker discusses an HIV treatment related topic. Entry is free. The next topic is 'Disclosure', and will be held on 27th March 2006. For more details, go to www.aidsmap.com/forums.

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