

aids treatment update



the future...now?

have the better drugs we've been waiting for actually arrived? *page 4*

genetic testing

why a cheap and simple test signifies the start of a brave new world *page 12*

can hiv really be cured?

the truth behind the hype *page 18*

drug-resistant hiv

why the future could be scary for the newly infected *page 3*

do ccr5 inhibitors have a future?

what happened to the most promising new class of anti-HIV drugs? *page 9*

news in brief

hiv survival increases on anti-HIV drugs *page 16*

uk and worldwide, hiv is on the rise *page 17*

in this issue

This bumper 20-page issue is all about the future of HIV treatment. On one hand, some people might argue that here in the UK we've never had it so good: we're seeing decreases in illness and death and a longer life-expectancy; more choice of simpler, easy-to-tolerate anti-HIV medicines and new technologies to help us avoid certain side-effects.

On the other hand, there's a worrying increase in transmitted HIV resistance that may mean people newly infected with HIV will have less, not more, treatment options in the future. Although there are some exciting new classes of anti-HIV therapies in the pipeline, only one new drug might be available in 2006, and only for very treatment-experienced people; little is on the horizon that appears to be significantly less toxic. And there's still no cure for HIV in sight.

The most significant, positive change in 2006 is the availability of a genetic test to see if you are likely to experience a really unpleasant side-effect of abacavir. If you are offered *Ziagen*, *Kivexa*, or *Trizivir* – all of which contain abacavir – make sure you ask for the test, pointing out that at £50, it's a small price to pay for a big benefit.

Here's to a happy and healthy 2006.

page 3 In *upfront*, Keith Alcorn examines the significance of increased transmission of drug-resistant HIV.

page 4 In *The Future...now?* Edwin J Bernard takes a look at the anti-HIV drugs that are available now, and those likely to be available soon, and asks whether current HIV therapy is the best we're likely to get for the foreseeable future.

page 9 In *Do CCR5 inhibitors have a future?* we ask what happened to last year's most promising new drug class?

page 12 Gus Cairns explains what genetic testing can do for us right now, and how it might help people with HIV in the future.

page 16 Amongst the items in *News in Brief*, we discover that although anti-HIV therapy is reducing illness and death in the US, the UK and in other western European countries, resulting in an increased life-expectancy for people who can tolerate long-term therapy, worldwide access to these drugs is still lacking.

page 18 After the tabloids hype an HIV cure, Edwin J Bernard asks the experts whether HIV really can be eradicated.



aids treatment update

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one in five newly infected people have drug-resistant hiv

by Keith Alcorn

The proportion of people who are being infected with a strain of HIV that is resistant to at least one anti-HIV drug has almost doubled in seven years, and the UK may now have the highest rate of 'primary' drug resistance in the world, according to a recently-published study of 2300 patients in the UK between 1996 and 2003^[1]. In 2003, one in five newly diagnosed individuals had acquired HIV resistant to at least one drug compared with just over one in ten in 1996. The implications of these findings for people newly diagnosed with HIV are disturbing, to say the least.

The first data on the high rates of transmitted drug resistance were published last year by the Health Protection Agency (HPA), which reported that 27% of gay men who had been infected in 2002 had a strain of HIV resistant to at least one drug. This study used a specialised version of the HIV antibody test that was able to identify people who had been infected less than six months previously, capturing cases of drug resistance before they faded into the background (only to reappear as soon as a specific drug is taken).

In the HPA study, two-thirds of those identified with drug-resistant virus had high level resistance to at least **one drug**, predominantly from the nucleoside analogue class (drugs like AZT, 3TC and abacavir). More worryingly, just under one-quarter had resistance to drugs from **two** different anti-HIV drug **classes**, suggesting that it might be difficult to assemble an effective second- or third-line regimen

without having to use the injectable drug T-20 – a prospect that may give pause for thought to anyone who believes that HIV treatment is now a simple matter of taking a couple of pills once a day.

The researchers estimated that 13% of first-line regimens started in 2002-2003 wouldn't work properly, possibly requiring people to take d4T, which is no longer recommended for first-line therapy as it is known to cause fat loss quicker than AZT.

The HPA also found that 39.5% of gay men recently infected with drug resistant HIV had an acute sexually transmitted infection (STI), suggesting that these men were especially infectious to others (most acute STIs increase the risk of passing on HIV).

But drug resistant HIV isn't just a gay issue. Surprisingly, the latest study found no difference between gay men and Africans living in the UK in the level of acquired drug resistance. This suggests that either rates of drug-resistant HIV transmission among Africans in the UK are much higher than previously thought, or that newly diagnosed Africans (or their sexual partners) are being exposed to brief periods of suboptimal treatment in other countries, before being treated in the UK.

Taken together, these findings spell out a number of important messages that need to be understood by anyone at risk of HIV infection and anyone living with HIV.

- Acquisition of drug resistant virus is likely to become more common as time goes by, because there are more people living with HIV and more HIV-positive people with resistance to at least one drug.
- Although drug-resistant virus does not cause faster disease progression if left untreated, having a strain of HIV that is resistant to one or more drugs means that you may not be able to take the most effective, best tolerated, easiest-to-take HIV drugs.
- Instead, you may have to start HIV treatment with drugs no longer commonly prescribed, which cause facial fat loss, other body fat changes, and/or chronic diarrhoea.
- If you are diagnosed HIV-positive or have been recently diagnosed, you should have received a resistance test. If not, ask your doctor for a test.

If you already have drug-resistant virus, you are more likely to pass it on to others through unprotected sex if you have:

- a detectable viral load
- a sexually transmitted infection, especially gonorrhoea or urethritis



the future... now?

Is the future of HIV therapy already here, or do we still have a long way to go? by Edwin J Bernard

Summary

- Anti-HIV drugs have improved somewhat in the past decade.
- However we still need new drugs that work against drug-resistant HIV strains and have fewer side-effects.
- The newest anti-HIV drug, tipranavir (*Aptivus*) is only approved for people with very few options, and should be used with T-20 (enfuvirtide, *Fuzeon*) to pack the biggest anti-HIV punch.
- Only one new drug might be approved this year, TMC114, and it appears to be similar to tipranavir.
- Studies are ongoing for new versions of current drug classes which should work against drug-resistant HIV.
- Integrase and maturation inhibitors are exciting new drug classes currently being studied.

It's been ten years since the current era of highly active antiretroviral therapy, or HAART, began. In 1996, it became clear that by combining one of the three recently-developed protease inhibitors - ritonavir (*Norvir*), indinavir (*Crixivan*) or saquinavir (*Invirase*) - with two of the existing nucleoside drugs, like AZT (zidovudine, *Retrovir*) and 3TC (lamivudine, *Epivir*), it was possible to prevent HIV from causing further damage to the immune system by stopping it from duplicating itself. For the first time, it was possible to get the amount of HIV in the blood down to extremely low levels, allowing the immune system to begin to repair itself, resulting in many previously very sick people returning to relatively good health.

Raising the bar

Those early HAART combinations were difficult to take, requiring three times-daily dosing and large numbers of pills or foul-tasting liquid. They also had a lot of food restrictions and caused unpleasant side-effects, like kidney stones and chronic diarrhoea. However, the people who got these first HAART combinations were so grateful to get them, since these life-saving drugs were in short supply, that they did their best to adhere to them because they felt they had no other choice.

A decade later, the bar has been raised dramatically, and we rightfully demand



much more of our anti-HIV therapy. We want a potent combination that fits in with our lifestyle, that is easy to take in terms of numbers and size of pills, as well as frequency; that doesn't have unbearable short-term or life-threatening long-term side-effects, and gives us more options if our HIV becomes resistant.

Everyone agrees that the current crop of anti-HIV drugs is nowhere near perfect - particularly when it comes to side-effects - but the drugs are already a vast improvement on what was available ten years ago, and couldn't even be conceived of by most people living with HIV twenty years ago. Is the future of anti-HIV therapy that was dreamed about in the first dark decade of HIV already here? Or do we still have a long way to go?

What we have now

There are currently 18 individually approved anti-HIV drugs in the UK (and Europe), available in over 40 different strengths and versions (not including paediatric formulations) including four fixed-dose combination tablets.

For people starting their first anti-HIV therapy combination in 2006, HAART can comprise just two pills - *Kivexa* or *Truvada* with efavirenz (*Sustiva*) once a day - with no food restrictions. However, this combination isn't always suitable for everyone and anti-HIV treatment may

become much more burdensome the further up the anti-HIV treatment ladder you climb. If your HIV has acquired resistance along the way, or you are unable to take the simpler combinations, major convenience trade-offs begin to occur.

True, if you need to take a protease inhibitor (PI), and your HIV is not yet resistant to PIs, you could still enjoy a low once-daily pill-burden if you took ritonavir-boosted atazanavir (*Reyataz*), but this needs to be with food. However, all other PIs are twice-daily, although fosamprenavir (*Telzir*) allows for the lowest pill-burden and no food requirements.

But if your HIV has become resistant to most drugs in several drug classes, then you may need to take an awful lot of pills, with food restrictions, and, in the case of T-20 (enfuvirtide, *Fuzeon*), self-inject under the skin twice a day.

First-line anti-HIV regimens may be getting easier to take but they still aren't necessarily any easier to tolerate. Last October, a British HIV Association audit of UK patients who switch from their first- to second-line anti-HIV therapy found that side-effects were the main reason people switched therapy^[1]. It makes sense, then, that new drugs with fewer short-term and less long-term side-effects ought to be developed.

Why do we need new drugs?

Although it appears that we have a greater choice of anti-HIV drugs, the British HIV Association's (BHIVA) latest treatment guidelines, in effect, give us fewer drugs to choose from, as more is known about the side-effects of some drugs. And for the first time, an anti-HIV drug is disappearing from the pharmacy shelves this year. One of the very first anti-HIV drugs, ddC (zalcitabine, *Hivid*) has now been discontinued by its manufacturer, Roche, because very few people were using it due to its strong association with peripheral neuropathy (nerve damage to the feet and hands).

Another 30% of patients in the recent BHIVA audit switched because their HIV had become resistant to their drugs, and earlier in the year, the UK Collaborative HIV Cohort (UK CHIC) reported that a small but growing proportion of HIV-positive patients in the UK may be in danger of exhausting current treatment options. "New drugs with low toxicity, which are not associated with cross resistance to existing drugs," are urgently needed for such patients, the study's authors argued^[2].

However, Dr Mike Youle, Director of Clinical Research at London's Royal Free Hospital and one of the UK CHIC's authors, now tells *ATU*, "There are very few people in this country that really need new drugs. I only have three people at the Royal Free who cannot



get their viral load 'undetectable' with currently available drugs, as long as they take their therapy."

Youle, who has a reputation for speaking his mind, concedes that taking currently available therapy isn't always as easy as he makes it sound, particularly when mental health issues, co-infection with hepatitis C, and/or those often intolerable side-effects get in the way.

NNRTIs

what else is new?

- GlaxoSmithKline's NNRTI, GW695634, seems safe and active in NNRTI-resistant patients, and is a rival to TMC278.



What's new now?

In the past few years, we've seen more new versions of existing drugs than actual new drugs, as drug companies fight for market share by trumpeting that their new formulation or combination pills are easier to take because they mean less pills less frequently and/or no food restrictions, and fewer or different side-effects. Only one new formulation is due to arrive in the UK this year. The new *Kaletra* tablet appears to have several advantages over the existing capsule formulation, since it doesn't require refrigeration, results in a lower pill-burden, and can be taken with or

without food. It also seems to result in fewer and less severe side-effects, like diarrhoea^[3].

The only new drug approved in 2005 was the PI tipranavir (*Aptivus*), which needs to be boosted with ritonavir, and which received UK and European marketing approval last October. However approval was only for people with extensive previous experience of antiretroviral therapy with HIV which is resistant to other PIs; it cannot be combined with any other PI, and more data are still required on its longer-term side-effects and drug-drug interactions. Manufacturer Boehringer Ingelheim has agreed to continue to investigate the drug in children, women and individuals co-infected with hepatitis, and tipranavir is also being studied in treatment-naïve people, but no data are available for now.

In addition, activists are outraged at tipranavir's price (it is the most expensive PI so far) and Dr Clifford Leen, Consultant in Infectious Diseases at Western General Hospital, Edinburgh, tells *ATU* that "its cost is likely to be a major limiting factor for widespread use." What makes tipranavir appear to be poor value for money are recent studies^[4] suggesting that whilst boosted tipranavir works okay when used with an optimised background regimen (individually chosen based on the results of resistance testing), the drug really packs a potent punch when combined with T-20 (enfuvirtide, *Fuzeon*), the most expensive anti-HIV drug, costing around £13,500 a year. Thanks to those studies, the revised US

treatment guidelines, published last October, now recommend combining boosted tipranavir with T-20 for maximum impact.

However, these US guidelines have also raised the bar for multiclass drug-experienced individuals, by suggesting that this combination makes the goal of 'undetectable' viral load a reality, when previously the goal of so-called 'salvage' therapy was to just keep patients alive until better therapies came along.

Dr Youle thinks that tipranavir and T-20 are the better 'salvage' therapies that we've been waiting for. "Some people are saying tipranavir is never going to be used, and they used to say that about T-20, but I think that if you use them cleverly they're very good drugs," he says. "I have a number of people on tipranavir and T-20 at the Royal Free who are 'undetectable' with no diarrhoea, no nausea, and no lipid changes." However, liver toxicity remains a concern.

Cost issues aside, persuading doctors to prescribe T-20, and people with HIV to self-inject twice daily, appears to be an uphill battle, according to two studies presented at the European AIDS Conference in Dublin in November, one of which was co-authored by Dr Youle. It seems that many people with HIV who might benefit from T-20 are still reluctant to accept self-injectable treatments due to fears about pain, inconvenience and it being a 'last resort'. However, in a chicken-and-egg conundrum, they may be more willing to consider self-injectable treatments than many doctors



believe, but only if their doctors recommend using it [5,6].

What's coming next?

The only new drug that may possibly become licensed this year is the protease inhibitor, TMC114 (darunavir), from Belgian company Tibotec, a subsidiary of Johnson & Johnson. Several different phase III studies are ongoing for this PI which also needs to be boosted with ritonavir. These include early access for treatment-experienced patients with few or no other options, as well several head-to-head comparisons with *Kaletra* for treatment-naive individuals, or those who have had some experience of PIs or the non-nucleoside reverse transcriptase drugs (NNRTIs), efavirenz (*Sustiva*) and nevirapine (*Viramune*).

which new drugs would I like in my medicine cabinet?
maturation and integrase inhibitors

If American and European drug regulators move quickly to review early data on TMC114, Tibotec hope to win accelerated approval for treatment-experienced patients by autumn 2006, putting TMC114 on an equal footing with tipranavir. Studies

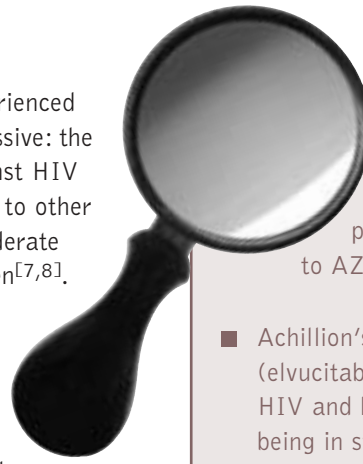
so far in triple-class experienced patients have been impressive: the drug appears active against HIV with high-level resistance to other PIs, and only mild to moderate side-effects have been seen[7,8].

"Our initial excitement with boosted TMC114 appears to be supported by recent reports that early benefits at six months are maintained," comments Leen, "but whether it should be used earlier will depend on current studies in patients with earlier disease."

Dr Youle, who has been giving TMC114 to some of his treatment-experienced patients, suggests cautious enthusiasm until more data emerge: "I wouldn't say it was the best drug in the world," he says, adding, "and right now I would not buy into the idea that it's stronger than tipranavir."

Another experimental Tibotec drug, the NNRTI TMC125, is also being studied intensely, although it will probably only be marketed as a 'salvage' drug. In late November, the company halted a study in PI-naive patients who had failed a first-line NNRTI, since the participants who took a PI did better after 12 weeks than those who took TMC125. This contradicts data reported at the European AIDS Conference held a week earlier, which had suggested this drug could be the first NNRTI to work after the development of efavirenz or nevirapine resistance.

"It's clear that TMC125 won't work for everyone," says Youle, "but the group of people that will most benefit from it are the people who have had to stop efavirenz or nevirapine due to



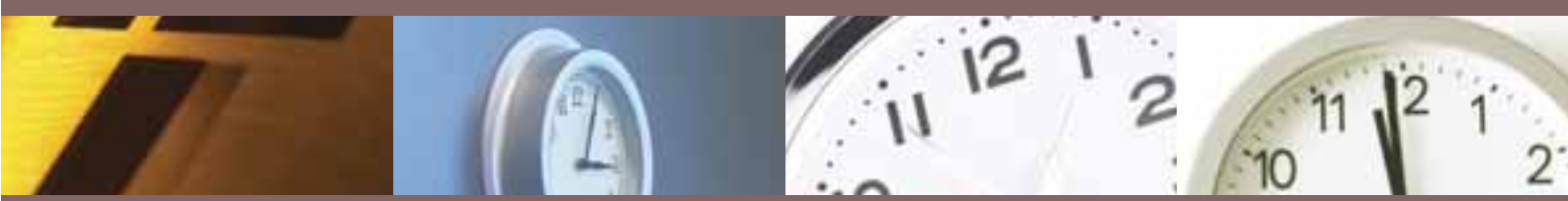
NNRTIs

what else is new?

- Pharmasset's D-d4FC (*Reverset*) is being studied in people with resistance to AZT and 3TC.
- Achillion's ACH126 (elvucitabine) works against HIV and hepatitis B, and is being studied in treatment-experience individuals resistant to 3TC and FTC with HIV and also those co-infected with hepatitis B.
- Pharmasset's PSI5004 (*Racivir*) may also work against HIV and hepatitis B, and is being studied in people resistant to 3TC and FTC.
- Avexa's AVX754 is also being studied in people resistant to 3TC and FTC.

toxicity, since it appears that rash [associated with currently approved NNRTIs] occurs less often, and central nervous system side-effects [like sleep disturbances, dizziness and depression, associated with efavirenz] doesn't appear to occur at all."

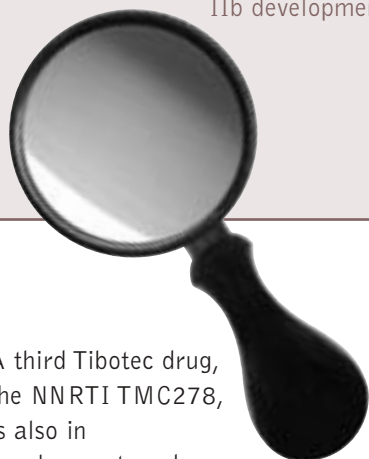
Undeterred, Tibotec is now enrolling phase III studies in highly treatment-experienced individuals (with at least three PI mutations and NNRTI resistance) that combine both TMC125 with boosted TMC114. This is the first time that two new investigational anti-HIV drugs have been studied together as 'salvage' therapy.



PIs

what else is new?

- GlaxoSmithKline's bucranavir (640385) has potent anti-HIV activity against both resistant and sensitive virus, when boosted by ritonavir and used with *Combivir*, according to eight week data from a 48 week study. It's now in Phase I Ib development.



A third Tibotec drug, the NNRTI TMC278, is also in development, and Youle thinks there's a place for both NNRTIs since early studies suggest that TMC278 is effective against HIV that is resistant to other NNRTIs, and it should be able to be dosed once daily. "TMC125 has the disadvantage of twice-daily dosing," Youle comments, "but I think by the time you've got to third-line therapy that's not a big issue. That's why they're developing both drugs: TMC125 for 'salvage' and TMC278 for earlier treatment. But, whilst TMC278 might be nice for people who've failed non-nukes, it's not going to be one of those drugs that revolutionises what we do, whereas I think integrase inhibitors could."

The future...on its way

Drugs to inhibit the third HIV enzyme, integrase - which splices HIV's genes into human cells - have been talked about ever since HIV's

life cycle was first understood. "Merck have been quite tenacious with integrase inhibitors," comments Youle. "They've worked on them for twelve years with no hard outcomes, and finally they've got a drug that seems to have promise." Although they reported earlier in the year on L-870810, it is MK-0518, "son of L-870810", that excites Youle. As reported at the European AIDS Conference in Dublin^[9], a ten-day study comparing this drug with an inactive placebo suggests that MK-0518 is potent and generally well-tolerated. Studies are now enrolling to compare it with efavirenz in treatment-naive individuals over 48-weeks.

"BMS and Gilead also have integrase inhibitors, and it's feeding frenzy time now," says Youle, "because once one company has a drug that is shown to be beneficial, the other companies will be pouring all of their resources into catching up."

Another new class is also at a similar stage of development, with Panacos Pharmaceuticals taking the lead with their maturation inhibitor, PA-457. Ten-day studies so far suggest it is potent and long-lasting, and larger studies should start very soon.

Maturation inhibitors reduce HIV viral load by interfering with the production of the HIV capsid protein. If this protein is not assembled, any HIV particles that are produced will be defective and unable to infect other human cells.

Dr Youle thinks that both classes are the most promising developments in HIV medicine for a long time. "If you asked me which drugs I'd like that I'd never had before in my medicine cabinet, it would be PA-457 and Merck's integrase inhibitor," he says. "There aren't that many other things around that I would be desperately interested in."

what else is new?

binding, fusion and entry inhibitors

- Progenics' PR0542, an attachment inhibitors which needs to be injected, is in phase II studies.



- Progenics' PR0140, a monoclonal antibody designed to bind to CCR5, also needs to be injected, and is in phase 1b studies.

- Tanox's TNX355, a monoclonal antibody given by intravenous injection, and which cuts viral load in multiclass-experienced patients, but no new studies are currently recruiting.



do CCR5 inhibitors have a future?

What happened to last year's most promising drug class?
by Edwin J Bernard

Summary

- In 2005, three drug companies began large studies of a new class of drugs, CCR5 inhibitors.
- CCR5 inhibitors block HIV from using a chemical that helps the virus invade CD4 cells
- Studies of one drug, *aplaviroc*, have now been discontinued, due to concerns over liver toxicity.
- Another drug, *vicriviroc*, is now only being studied in people who have taken anti-HIV therapy before.
- One person on *maraviroc* had very serious liver problems, although they probably weren't caused by the drug, and all studies are continuing.
- Initial enthusiasm for this class of drugs has waned, but they could still prove to be very useful.

Last May, *ATU* examined the newest class of antiretrovirals on the development fast-track, CCR5 inhibitors. At the time it appeared to be a three-horse race between GlaxoSmithKline's *aplaviroc* (GW873140), Schering Plough's *vicriviroc* (SCH-D) and Pfizer's *maraviroc* (UK-427), to bring the first CCR5 inhibitor to market.

These drugs promised to become the first oral anti-HIV drugs that could prevent HIV from entering cells. They would do this by blocking HIV from using the body's own chemical, a chemokine known as CCR5, that HIV uses to attach to CD4 cells.

It was hoped that, since CCR5 inhibitors do their work outside of cells, they would produce fewer side-effects than most of the currently available anti-HIV drugs, which, with the exception of T-20 (*enfuvirtide*, *Fuzeon*), work inside cells.


However, there were concerns that these drugs had the potential to make people sicker, by forcing HIV to use another chemokine, CXCR4, which results in HIV being more aggressive and disease-causing, and is associated with the later stages of HIV disease and AIDS.

In addition, some European patient advocates, the European AIDS Treatment Group (EATG), were concerned that Pfizer might enrol treatment-naïve individuals with very low CD4 counts into one of their *maraviroc* studies. They argued that people new to therapy who were very sick ought to get currently-approved drugs that are known to work, and not enter a clinical trial for a drug about which precious little was known. However, US patient advocates sided with Pfizer when they said that the study "includes appropriate checks and balances to protect patient safety".

It's over for *aplaviroc*

The first sign that the course was hard-going came last September, when GlaxoSmithKline announced the





termination of their phase IIb studies of aplaviroc in treatment-naïve individuals following reports of severe liver toxicity. At the time they said that studies in treatment-experienced patients would continue, subject to close monitoring of the participants. A month later, however, GSK announced that it was calling

a halt to those studies, too, due to another case of liver toxicity: in total four cases had been seen.

All four involved abnormalities in two types of liver function tests. In one, levels of alanine aminotransferase (ALT) were three times the upper limit of normal. In the other, levels of bilirubin were one and a half times the upper limit of normal. That combination of liver test abnormalities is very worrying, since it is thought that high ALT with high bilirubin could lead to fatal liver failure 10% to 50% of the time.

Fortunately, all the liver problems resolved when the four people taking aplaviroc stopped the drug. When one person restarted, the problems returned, confirming that aplaviroc was indeed the cause.

Consequently, GSK is not planning any further studies of this drug, although other CCR5 inhibitors are being developed in the GSK stable.

Vicriviroc stumbles

A week before GSK announced the termination of their aplaviroc studies, Schering Plough halted a phase II

study of vicriviroc in treatment-naïve individuals because of early viral load rebound in some of the patients receiving the drug. The company announced in a press release that it had discontinued its phase II treatment-naïve study following a recommendation from the independent Data Safety Monitoring Board (DSMB) which has been meeting regularly to conduct reviews of the safety and efficacy data.

It stressed that the decision wasn't due to liver toxicity. In fact, the increased incidence of detectable virus was only seen in some of study participants after several weeks of treatment on vicriviroc with AZT/3TC (*Combivir*) compared with the people in that study who were using *Combivir* and efavirenz (*Sustiva*).

A phase II study involving treatment-experienced individuals is continuing, for now, but some doctors already believe that vicriviroc will not make it to the finishing line due its perceived lack of potency.

"I think it could be a dose issue," comments Dr Mike Youle, who notes that there is always the risk that people may get less than therapeutic doses in these early studies. "People get very concerned about taking a drug that may be sub-therapeutic and may give you resistance."

However, although early studies of Roche's protease inhibitor (PI), saquinavir (taken alongside ddC), led to many participants developing cross-resistance to most PIs because less than 4% of the original

formulation was absorbed, the drug's development continued.

Since then, saquinavir has been through two major formulation changes and now, when saquinavir is boosted with ritonavir, it's a highly potent PI with a low chance of resistance emerging after virological failure in people who take anti-HIV therapy for the first time^[1].

Maraviroc jitters

In October, Pfizer announced that maraviroc had received the go-ahead to continue both phase III and phase IIb studies in treatment-experienced and treatment-naïve individuals, respectively, from the DSMB. But during the European AIDS Conference in Dublin, Pfizer announced that a "serious adverse event" had occurred in one treatment-naïve individual, leading to much rumour and speculation that the race was over with no winners.

However, since more details were reported a few weeks later at the First International Workshop on Inhibiting HIV Entry in Bethesda, Maryland, Pfizer's drug is back in the race, and looking like a strong contender. It now appears that this case of serious liver toxicity - the first seen in over 1300 individuals exposed to maraviroc - may have little to do with maraviroc.

The individual was both HIV and hepatitis C virus (HCV) positive, with some evidence of liver enlargement at the time the person entered the study. Seven weeks before starting on maraviroc, with normal liver function tests, the patient began isoniazid and cotrimoxazole

(*Bactrim/Septin*) to prevent TB and PCP pneumonia, respectively. Within a few weeks, and before starting on maraviroc, the patient's ALT levels were found to be three-times the upper limit of normal. However, this is not unusual on isoniazid.

After four doses of maraviroc, taken together with *Combivir*, on day 5 the patient developed a rash and fever, and maraviroc was discontinued and replaced with *Kaletra*. However, on day 6 the patient's ALT was 32 times the upper limit of normal, and was started on intravenous paracetamol. After a liver biopsy on day 9 an independent expert reported that the patient had developed severe drug-induced liver injury. This was, he said, most likely to be caused by isoniazid or cotrimoxazole, although maraviroc may have played a role.

The patient received a liver transplant on day 14, and the most recent reports suggest that this person is now clinically stable. Meanwhile, the DSMB, having reviewed all the data, concluded that the other medications administered during this episode appear more likely to be associated with the liver toxicity, although they could not definitively rule out that maraviroc had a role in this patient's illness.

Consequently, the DSMB has recommended various changes to the current maraviroc studies, including the exclusion of isoniazid, additional liver function tests during the screening period, and the immediate discontinuation of all study drugs and all potentially liver toxic drugs if treatment-naïve patients have liver

function tests greater than five-times the upper limit of normal.

What now?

"The initial enthusiasm with CCR5 inhibitors has been dampened by recent reports of liver toxicity related to aplaviroc and lack of potency of vicriviroc," comments Edinburgh HIV consultant, Clifford Leen. "And the report of a single case of severe liver toxicity in a patient taking maraviroc was alarming and threatened its clinical development, although current experience with maraviroc, though limited, suggests that it is clinically potent and useful."

Dr Youle puts it more bluntly. "It looks terrible for maraviroc," he says. "But when you delve in there I don't think it is terrible for maraviroc. We have half a dozen patients on maraviroc and we've taken another look at their liver function tests, and everything seems fine. What is comforting," he continues, "is knowing that the DSMB reviewed all the grade 1-4 liver toxicity in the study, and apart from this one case, there appears to be no serious liver problems."

Does Youle agree with the European patient advocates who voiced fears last year that the race to get CCR5 inhibitors to market may harm some patients?

"I don't think there's any evidence of that at all," he says. "Although I agree, to some degree, with the EATG's concerns about the way the study was designed, I'm more concerned about killing drugs by hearsay, or the odd case, before all the evidence is in."

Both Leen and Youle believe it's too early to write off the CCR5 inhibitor class, and in particular, maraviroc, but they know that the final hurdle has yet to be reached.

"The use of maraviroc may be limited by difficulties in our understanding of HIV coreceptor usage and by technical difficulties in determining coreceptor usage as well as the five to six weeks it takes to determine tropism [whether a person's HIV is mainly using CCR5 or CXCR4 to attach to cells]," says Leen. "Should maraviroc be used early when we think that most of the virus is CCR5 tropic, as opposed to later when CXCR4 usage is likely to be higher? It is too early to say."

"Until we get a CXCR4 inhibitor to go with these CCR5 inhibitors, there remains a question about how best to use CCR5 inhibitors," adds Youle. Currently, only one CXCR4 inhibitor is in development, Anormed's AMD070, and since it is only in early phase I/II studies, data are scarce.

"I think there's going to be some very interesting times ahead," says a confident Youle.

"Other companies have other entry inhibitors, including CXCR4 inhibitors, other fusion inhibitors, receptor blockers, and they are watching what happens with CCR5 inhibitors like hawks. The next six months is not only going to be interesting," he concludes, "but also quite important for the future of HIV drug development."

Summary

- A new test is now available in some parts of the UK to test for a gene that is associated with hypersensitivity to abacavir (*Ziagen*), also found in the combination pills, *Kivexa* and *Trizivir*.
- This is the first time that genetic testing has been used in the HIV clinic, and it should be available to everyone in the UK in 2006, either as routine testing or as part of a clinical trial.
- Genetic testing may also be used in the near future to predict who might get liver problems on nevirapine (*Viramune*).
- It is hoped that we could eventually use genetic tests to help develop an HIV vaccine.



On World AIDS Day, December 1st 2005, a small but extremely significant announcement for people living with HIV in the UK was made by the people who agree to pay for HIV treatment in London.

The London HIV Consortium announced that they will pay for a new genetic test for a gene called HLA B*5701 that is associated with the hypersensitivity reaction to the anti-HIV drug abacavir, which is found in single pill form (*Ziagen*), the dual combination pill, *Kivexa* (with 3TC), and the triple combination pill, *Trizivir* (with AZT/3TC).

This should lead to all UK clinics following suit, resulting in this sophisticated but relatively cheap (around £50) and simple test becoming part of the standard of care for HIV in 2006. If this is the case, it will be the first time that genetic testing will have been routinely used in the clinic to predict how people's bodies will react to a specific drug.

Abacavir and hypersensitivity

Current British HIV Association (BHIVA) treatment guidelines make it clear that their preference for people starting anti-HIV treatment in 2006 is to combine the nucleoside reverse transcriptase inhibitors (NRTIs) 3TC (lamivudine, *Epivir*) or FTC (emtricitabine, *Emtriva*) with either tenofovir (*Viread*) or abacavir (*Ziagen*) as the two background NRTIs in a triple drug anti-HIV regimen. In practice, this means first-timers are increasingly likely to be offered a choice between two dual-NRTI fixed-dose combination pills as part of their first regimen: *Truvada* (tenofovir/FTC) or *Kivexa* (abacavir/3TC).

genetic testing

What it can do for us now and in the future, by Gus Cairns

No anti-HIV drug is risk free, and tenofovir is not without some safety concerns. Fortunately, many studies have now disproved predictions that it would cause frequent kidney toxicity, instead suggesting that the mild kidney dysfunction that can be seen in blood and urine tests appear to cause no short-to-mid-term harm in people with healthy kidneys^[1]. However, people who already have kidney impairment shouldn't use tenofovir.

Truvada is also about a third more expensive than *Kivexa* in the UK, and for the first time, the 2005 BHIVA guidelines mention cost as a factor to be taken into account when deciding on which drugs make up an anti-HIV combination.

Abacavir's main drawback is the hypersensitivity reaction. This severe immune-system reaction to the drug causes fever, rash, nausea, vomiting, diarrhoea, and abdominal pain, sometimes with joint pain and swollen glands, usually within the first six weeks of starting abacavir. The hypersensitivity reaction is particularly dangerous if the drug is stopped and then restarted (known as 'rechallenge').

It's not always easy to diagnose the abacavir hypersensitivity reaction, and sometimes unusual hypersensitivity reactions have even been mistaken for tonsillitis^[2].

Abacavir's manufacturers, GlaxoSmithKline (GSK), estimate that overall about 5% of patients given abacavir have had a hypersensitivity reaction. Although there have been some deaths (31 out of 41,000 people who have taken abacavir since it was first made available), these mostly occurred pre-2004 when patients were

rechallenged, something that rarely happens now thanks to better doctor and patient education. Nevertheless, it's clearly a reaction to be avoided, and probably the major reason HIV doctors had been relatively sparing in their use of what is, otherwise, a drug with few apparent long-term side-effects.

It became clear to a number of scientists that a test to predict who would get the hypersensitivity reaction would allow doctors to be able to prescribe it with more confidence, and it would mean less anxiety and suffering for patients.

"I've only had two occasions where a patient has come to me and said: 'How could you put me on that awful drug?'" recalls HIV physician, Professor Simon Mallal - Director of the Centre for Clinical Immunology and Biomedical Statistics in Perth, Western Australia - who discovered the link between the abacavir hypersensitivity reaction and HLA B*5701. "One was someone who'd had a hypersensitivity reaction to abacavir."

"We've now virtually eliminated immunologically mediated abacavir hypersensitivity as an issue in Perth," he adds, "by testing for the gene that causes the reaction." However, he warned that another rare HLA type could yet be found that also mediated the reaction and that further studies were required before the test could be considered reliably predictive in more diverse ethnic populations.

Immune systems and PIN numbers

Professor Mallal had been investigating the variations in a series of genes responsible for making

proteins, called HLAs - Human Leukocyte Antigens. The HLAs are the body's system for distinguishing between 'self' and 'non-self' - between the body's own substances and foreign invaders. They are grooved molecules like hands that dot the surface of cells, and their job is to display in their 'palms' so-called epitopes, which are samples of the contents inside, to the patrolling cells of the immune system.

"The 'killer' CD8 cells seek out and destroy virally infected cells throughout the body by recognising small pieces of the virus within the HLA molecule," he explains. "Once the virus mutates to subvert this interaction with the HLA molecules it can grow unmolested by the immune system."

We have evolved a vast number of HLA types in response to these types of infectious diseases making it much harder for infections to sweep rapidly through the population. In effect, this has given each of us a fairly unique PIN number for our immune system which a virus such as HIV has to try and crack anew in each person by trial and error.

"We knew the abacavir hypersensitivity reaction had to be an HLA-mediated reaction because it's what's called a type B reaction," says Mallal. Type B reactions are not dose-dependent: the immune system mounts a disproportionately huge reaction to tiny doses of drug. This can be very dangerous, especially after a rechallenge.

What Mallal discovered was that there was only one out of the 2,280 known HLA types that mediates abacavir hypersensitivity: HLA B*5701.

The reliability of the B*5701 test

The B*5701 HLA varies in frequency between people of different ethnicities. Although it's more common amongst Caucasians than people of African or Chinese ethnicity, people of all ethnicities may still suffer a hypersensitivity reaction.

Mallal first tested his Perth patients in 2001 and presented his findings at the Retrovirus Conference in 2002^[3]. Only about 2% of patients who tested positive for HLA B*5701 did not get the hypersensitivity reaction. However, it also appeared that one in four patients testing negative for B*5701 still suffered the hypersensitivity reaction. At the time Mallal told the conference that HPA B*5701 testing "cannot be considered a screening test."

A larger study by GSK announced at the same conference produced even less reliable results^[4]. In hindsight, Mallal concedes that there were some over-zealous hypersensitivity reaction diagnoses in these studies: patients who had recently started abacavir were coming in with fevers and stomach upsets, and doctors, understandably vigilant, assumed they were caused by the drug.

These over-diagnoses were confirmed when the results of a large study comparing the triple-NRTI pill *Trizivir* (abacavir/3TC/AZT) with indinavir/3TC/AZT were analysed^[5]. Researchers found a rate of hypersensitivity reaction in abacavir-taking patients of 8%, and in patients not on abacavir of 3% - meaning that about 38% of so-called abacavir hypersensitivity reactions were probably due to something else.

This led to a tightening-up of the diagnostic criteria for a true hypersensitivity reaction, which, combined with the B*5701 test, meant that Mallal started seeing true hypersensitivity reactions increasingly less often: a rate of 7% in 2000/1 fell to 2% in 2004/5.

"One of those patients was someone where we did find a positive B*5701 test but the patient's physician hadn't spotted it in the notes," says Mallal. "Now we have a safeguard where the lab informs the pharmacy to prevent those errors."

It is now also possible to confirm if something that looks like a hypersensitivity reaction is a true abacavir reaction. This is done by a so-called 'patch test'. In this simple and safe procedure different dilutions of abacavir are dissolved in petroleum jelly and placed on the skin under

allergic to abacavir?

The most serious side-effect of abacavir is a severe allergic, or hypersensitivity, reaction which may be life-threatening. Although the symptoms vary, most cases involve a fever. Other symptoms include rash, nausea, vomiting, diarrhoea, and abdominal pain. Less common symptoms include lethargy, muscle or joint pain, headache, numbness on the skin, puffiness of the throat, face and neck, swollen glands, conjunctivitis, mouth ulcers and low blood pressure. Rash and gastrointestinal symptoms are more common in children experiencing a hypersensitivity reaction.

Although respiratory symptoms (shortness of breath, difficulty breathing, cough and sore throat) have been named as signs of abacavir hypersensitivity, a recent study found that they are not reliable indicators of hypersensitivity. The key difference between hypersensitivity and influenza is the presence of stomach symptoms like vomiting, diarrhoea, and abdominal pain in abacavir hypersensitivity.

Typically, a pattern of symptoms builds up over a period of days, often worsening as successive doses are taken. The hypersensitivity reaction is most commonly seen in the first two to six weeks of taking the drug, although cases after only one dose have been reported. However, as

hypersensitivity can occur at any time during abacavir treatment, all abacavir users should familiarise themselves with the symptoms of the reaction and notify their doctor immediately if they develop.

It is recommended that people starting abacavir are monitored very closely for the first two months of therapy, with consultation every two weeks. If a person who has recently started abacavir develops at least two symptoms associated with hypersensitivity, abacavir should be discontinued as soon as a formal diagnosis has been made by the patient's doctor. Abacavir should not be stopped in the absence of medical advice.

Once abacavir has been stopped because of hypersensitivity, the drug must never be taken again as re-starting in these circumstances can cause the allergic reaction to reappear within hours in a much more severe form. This can result in low blood pressure and death. Re-starting abacavir at a low dose following a hypersensitivity reaction is not considered safe and is not recommended.



we've virtually eliminated abacavir hypersensitivity as an

small plaques. If red bumps appear in 24-48 hours then you have a sensitivity to abacavir. But, importantly, this can only be done once someone has already experienced a hypersensitivity reaction - it's a confirmatory test, not a predictive one.

Getting it to the clinic

Some UK HIV clinics have actually been performing B*5701 testing since the middle of last year, including London's Chelsea and Westminster Hospital.

"We are doing an audit to make sure it's being used properly and rigorously," says clinical director Professor Brian Gazzard, who also heads London HIV's Consortium Drugs and Treatment Subgroup. "So far there has only been one death in a patient who was known to have B*5701. But GSK is worried that with this test we might be less vigilant about watching out for hypersensitivity reaction in patients new to abacavir. We don't want an excellent test to result in doctors relaxing their standards."

In order to make sure that GSK can stand by the test, and to ensure that it conforms to a single standard, GSK are sponsoring a randomised study that will include 2000 patients in Europe and Australia (100 in the UK) where half are given abacavir without the B*5701 test, while the other half are given the test, and abacavir is withheld if they test positive. If patients without B*5701 appear to suffer from a hypersensitivity reaction, patch testing will be done to confirm if it's a true reaction.

However, Dr Martin Fisher, of Brighton and Sussex University Hospitals, has doubts whether this study will fully enroll. "I'm not sure how well the GSK study will take off in the UK," he says. "Like many centres we are now doing B*5701 testing as routine and therefore would

not be happy to randomise people to receive abacavir without it."

Professor Gazzard admits that part of the reason that B*5701 testing has been approved in London is because of cost. "Tenofovir and abacavir are both good drugs, especially in first-line regimens," he says. "But at present *Truvada* is about a third more expensive than *Kivexa*, but we use *Truvada* six times for every four times we use *Kivexa*, because of concerns over the hypersensitivity reaction.

"By routinely offering and standardising the B*5701 test," he argues, "we can now use *Kivexa* more often, and offer *Truvada* to patients who are likely to have a hypersensitivity reaction to abacavir."

Testing for nevirapine hypersensitivity?

Could similar tests be used to rule out other drug side effects? Nevirapine (*Viramune*) is another drug which has caused fatal hypersensitivity reactions in the first six weeks of use, but which seems relatively free of side-effects thereafter.

Nevirapine causes two acute problems. The first is a rash, experienced by about one in six, although this is severe in about 7%, and 1% may get the very nasty Stevens-Johnson syndrome, which resembles severe skin burns.

The second is liver toxicity. Although there have been relatively few reactions in people with lower CD4 counts, women with CD4 counts over 250 and men with CD4 count over 400 are thought to be at an increased risk of liver toxicity, and are recommended by the manufacturer to avoid nevirapine.

However, there is an HLA subtype associated with nevirapine liver toxicity called DR*0101. "The problem with DR*0101 testing is that lots of things can cause liver toxicity," explains

Professor Mallal. "And the rash alone without fever or liver toxicity may be associated with the DR*07 HLA type or - especially with Stevens-Johnson syndrome - be associated with a different series of HLAs. You would still get a lot of people with real or coincidental toxicity if you only gave nevirapine to people without DR*0101. However it is reasonably predictive of liver toxicity and if I have a patient with a high CD4 count and see a positive benefit of using nevirapine - such as an inability to tolerate efavirenz - I do use the test."

The future?

Further in the future, HLA testing may be crucial in developing an HIV vaccine. Professor Mallal's colleague, Philip Goulder, has been testing hundreds of HIV-positive women for HLA types and is examining the relationship between HLA types and HIV viral load. He found that some HLA types were much better at controlling viral load, because they better alerted the immune system to HIV infection. One of the types that did this most efficiently was, in fact, B*5701.

Goulder discovered that there was an 'arms race' going on between the HLA molecules and HIV. HIV was mutating to escape the HLA alarm system - but in turn there was evidence that the HLA molecules had themselves mutated over the eons. Some of these mutated HLAs had surveillance abilities that made HIV much more susceptible to the immune system. Scientists like Goulder and Mallal are trying to exploit the advantage of our extraordinary HLA diversity to design more effective vaccines.

So, if you test positive for B*5701, although you won't be able to take abacavir you will almost certainly take longer than average before you need to start treatment at all. ■

issue in perth by testing for the gene that causes the reaction

news in brief

latest research



studies find deaths due to hiv are declining thanks to better drugs

Three studies from the United States, Europe and the United Kingdom have all concluded that better anti-HIV therapy has resulted in significant declines in death from HIV-related disease in the past decade. And a fourth study, from France, has found that HIV-positive people on successful treatment have the same mortality rate as their HIV-negative counterparts.

The US study found that hospital admissions and deaths amongst HIV-positive patients fell dramatically between 1996 and 2000. Here, the investigators looked at data from over 300,000 hospital admissions from twelve US states following the introduction of potent antiretroviral therapy in 1996. They found that the odds of dying with HIV were 30% lower in 2000 than in 1996. They also found that the reasons why individuals were admitted to hospital changed significantly, with opportunistic infections causing proportionately fewer admissions and liver-related illnesses proportionately more.

Adding to the data on liver-related illness, investigators from the large EuroSIDA study found that, although the overall death rate from liver-related disease fell after 1996, there was still a significant year-on-year increase in the rate of deaths once CD4 cell count was taken into account. They found that the length of time HIV-positive people co-infected with hepatitis B virus and/or hepatitis C virus took anti-HIV therapy was significantly associated with an increased rate of liver-related death. The investigators explain that this might be due to the fact that co-infected people are living longer with HIV, only to succumb to hepatitis, or because anti-HIV

therapy is also toxic to an already damaged liver, or a combination of both factors.

Data from London's Royal Free Hospital helps to put these liver-related deaths into perspective, however, since here only 3% of deaths in HIV-positive people between 1998 and 2003 were attributable to hepatitis B or hepatitis C virus infection. During that period, the rate of death per year in HIV-positive people fell by half, from 2% to 1%. Less than half of all deaths (46%) were due to HIV/AIDS, with another 4% attributable to the side-effects of anti-HIV therapy. Another 28% of deaths were due to causes unconnected to HIV infection and 22% were due to unknown causes. The investigators say that deaths due to HIV/AIDS were most likely to happen to people testing for HIV too late; waiting too long to use anti-HIV therapy; previously taking treatment combinations that would now be considered suboptimal; and resistance to anti-HIV drugs.

Finally, data from the French Aquitaine Cohort confirm that when you are able to stay on current anti-HIV treatments, and they work well, your risk of dying is pretty much the same as someone of the same age and gender who is HIV-negative. Between 1997 and 2003, one-in-four people who took protease inhibitor-based anti-HIV therapy maintained a CD4 cell count of over 500 cells/mm³ and viral load below 10,000 copies/ml, and only 0.7% died. This translated into a mortality rate that was only 10% above normal and one not significantly greater than the general HIV-negative population.

the new hiv news update from nam

news from *hiv weekly*

Control of HIV without HIV drugs

Only about 7% of HIV-positive people experience control of their viral load without anti-HIV treatment, a study has shown.

The study showed that women were more likely to experience control of viral load than men, as were people who did not experience a "seroconversion" illness soon after they were first infected with HIV.

People who had an undetectable viral load without treatment also had higher CD4 cell

counts. Researchers also found that people with an undetectable viral load without treatment were less likely to progress to AIDS.

However, control of viral load without treatment lasted for an average of just less than a year. Once control of viral load was lost, the CD4 cell count fell at a similar rate to that seen in other patients.

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



statistics

hiv on the rise throughout UK and worldwide

Over 40 million people are living with HIV worldwide, according to figures released by UNAIDS, who estimate that there were five million new infections in 2005. However, UNAIDS also estimate that only about 10% of HIV-positive individuals worldwide have taken an HIV test, and therefore know that they are infected with the virus.

Although more people than ever before received anti-HIV treatment in 2005, only a fraction of people who needed treatment were receiving it. In southern Africa, only 10% of HIV-positive individuals who needed them were treated with anti-HIV drugs this year, and only one in seven received treatment in Asia. Most of the three million HIV-related deaths which occurred in 2005 could have been prevented with appropriate HIV treatment, UNAIDS stresses. However, thanks to treatment access programmes, between 250,000 and 350,000 HIV deaths were prevented due to improved access to anti-HIV drugs last year.

In the UK, there are now more than 58,000 people living with HIV, and in 2004 there were 7272 new HIV diagnoses, which includes people who have been infected for some time as well as those more recently infected. The UK's most startling statistic, however, is that about one in three of all HIV-positive people don't know they are infected because they haven't taken an HIV test, according to a report from the Health Protection Agency (HPA). Undiagnosed - and therefore untreated - HIV is one of the main reasons people with HIV are still dying in the UK. It also greatly increases the chances of HIV transmission.

The report's authors suggests that the state of the UK's sexual health is in "a worrying situation with undiminished and high levels of transmission of HIV and other sexually transmitted infections (STIs) among men who have sex with men (MSM), a steady increase in the number of HIV-infected black Africans in the UK, limited but compelling evidence that heterosexual transmission of HIV within the UK is slowly rising, and continuing high transmission of other STIs, especially chlamydia among young people."

"It is essential that prevention messages are reiterated particularly to young people, MSM and to people residing in the UK who originate from HIV endemic areas", they conclude.



latest research

ritonavir to blame for most blood fat problems

A small Canadian study in HIV-negative people has found that the increased blood fat levels often observed in HIV-positive individuals prescribed lopinavir/ritonavir (*Kaletra*) are almost entirely caused by the 100mg twice-daily dose of ritonavir included in the orange capsule. Low-dose ritonavir (ranging from 100mg to 400mg daily) is currently used to boost levels of most available and experimental protease inhibitors (PIs), including *Kaletra*, the most frequently prescribed PI in the UK, but until now doctors have only guessed at the relative contribution of the ritonavir boost to high blood fat levels. The study's authors suggest that ritonavir-boosted PIs should be reserved for second-line or later therapy if other options are available for first-line therapy but argue that the anti-HIV potency of boosted PIs when fewer options are available outweighs the cardiovascular risks of raised lipids. They also suggest examining whether doses less than 200mg ritonavir daily could be used as a boosting agent, and note that atazanavir (*Reyataz*), which is associated with less blood fat problems, is already being given with just 100mg ritonavir daily.

can hiv be cured?

by Edwin J Bernard

The media hyping of a cure for HIV didn't begin with the chequebook journalism story of "miracle man" Andrew Stimpson and his premature claims that he was "cured" of HIV last November. Nevertheless, Stimpson's story relit the fire under the burning question that has been on everyone's mind since AIDS was first described: can HIV can really be cured?

Right now it is too early to speculate whether Mr Stimpson's case means he was cured, or whether there were lab or other errors in his diagnoses. What we do know is that scientists have been working on eradicating HIV from the body for more than a decade, and although knowledge is increasing, so far their work has been disappointing. Back in 1996 Dr David Ho thought that it was possible for currently available anti-HIV drug combinations

to eradicate HIV. It is now thought that although current drugs may be able to reduce HIV to 'undetectable' levels in the blood, they cannot remove HIV's genes that are integrated in the DNA of our own cells.

Scientists have now established that a small proportion of HIV-infected cells do not die, but become dormant all over body in places known as 'sanctuary sites' or 'viral reservoirs', which include lymph nodes and lymphatic tissue; the gastrointestinal tract, from the tonsils to the rectum; the central nervous system; the thymus, where T-cells are educated, mature and multiply; and the testicles. Anti-HIV therapy cannot kill them in these places because the HIV-infected cells are not actively producing new HIV particles.

Is valproic acid a cure?

The scientific journal, *The Lancet*, engaged in its own, more subdued version of hype earlier in the year, when it suggested on its cover that a small proof-of-concept study showing that the drug valproic acid (*Depakote*) was able to substantially reduce these viral reservoirs in the body, and might

eventually point the way towards a cure for HIV infection^[1]. However, although the study was a step in the right direction, most experts agree that many years of further research are required before they can effectively find a way to 'flush out' 100% of all hidden stores of HIV.

ATU asked two of the world's experts on viral reservoirs where we are in terms of eradicating HIV. Dr Robert Siliciano, from Johns Hopkins University, was one of the scientists who discovered viral reservoirs in the mid-1990s. Dr Tae-Wook Chun from the US National Institutes of Health has been studying eradication for many years, and recently published a paper in the *Journal of Clinical Investigation* which shed new light onto why individuals who have persistently maintained an 'undetectable' viral load, are still unable to eradicate HIV^[2].

ATU: Valproic acid received a lot of media attention last year. Could it lead to a cure?

Dr Tae-Wook Chun (T-WC): Personally, I think it is too premature to say so. *The Lancet* paper presented only two time points after administering valproic acid.

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one in five newly infected people have drug-resistant hiv [page three]

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You need a lot more time points to address the decay characteristics of the latent viral reservoir. A clinical trial needs to be conducted to accurately address the efficacy of valproic acid in eliminating infected cells.

Dr Robert Siliciano (RC)^[3]: Because few investigators have been willing to speculate on a cure in recent years, this report received a great deal of attention in the lay press and stimulated many inquiries from curious patients. It is important, therefore, to put this work in perspective. While the search for ways to eliminate viral reservoirs is clearly essential to finding a cure, there are several reasons why speculation about a cure is premature. First, it is not entirely clear that the results will hold up in a larger study carried out over a longer time frame. A second major issue involves the underlying rationale for using valproic acid: latency is complex, and it is not clear that valproic acid alone will overcome other blocks to HIV production in resting CD4 T-cells. A third problem is that valproic acid only led to partial reductions in the size of the latent reservoir. Eradication would require a >99.9999% reduction in the reservoir.

ATU: Does anything else come close to reducing the HIV reservoir as much as valproic acid? Even if we can't eradicate HIV is there any benefit to flushing out the viral reservoir?

T-wc: We've tried anti-CD3 antibodies and interleukin-2 to stimulate the latent viral reservoir. Both approaches failed.

RS: Even if a cure cannot be achieved, understanding viral reservoirs can contribute to the management of HIV infection. One critical issue is the ability of the latent reservoir in resting CD4 T-cells to store drug resistant virus. So even if approaches for eliminating the reservoir cannot be developed in the near future, some comfort can be taken from the fact that HAART appears capable of fully arresting virus evolution in adherent patients. Thus, with optimal treatment, patients should be able to expect a normal life span.

ATU: Finally, do you think eradication of HIV from the body will happen in our lifetime?

T-wc: I personally think that it will be extremely unlikely to completely eliminate latently infected CD4 T-cells. It's a numbers game. The frequency of latently infected, resting CD4 T cells could be as low as 0.001 per million

cells. So, it would be very difficult to hit those infected cells no matter what agents you use. It would be possible only in a subset of infected patients, such as those who initiated therapy early in infection and who have been on therapy for over 8-10 years.

RC: We have been working on this problem for ten years and have made no real progress. My feeling is that it will not be possible in the next 10-20 years.

further information

For more on the eradication of HIV, read 'Eradicating HIV?' on aidsmap.com, or in the 2006 'HIV and AIDS Treatments Directory' (£12.95 for individuals affected by HIV, £64.95 for professionals), available from the Publications Centre on aidsmap.com, or by calling NAM on 020 7840 0050.



genetic testing [page twelve]

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Studies find deaths due to HIV are declining thanks to better drugs

- 1 Gebo KA et al. *Hospitalizations for metabolic conditions, opportunistic infections, and injection drug use among HIV patients: trends between 1996 and 2000 in 12 states*. J Acquir Immune Defic Syndr 40: 609 - 616, 2005.
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Ritonavir to blame for most blood fat problems

- 1 Shafran SD et al. *The effect of low-dose ritonavir monotherapy on fasting serum lipid concentrations*. HIV Med 6(6): 421-425, 2005.

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- 1 Madec Y et al. *Spontaneous control of viral load and CD4 cell count progression among HIV-1 seroconverters*. AIDS 19: 2001-2007, 2005.

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Where to find out more about HIV

■ Find out more about HIV treatment:

NAM's factsheets, booklets, directories and website, keep you up to date about key topics, and are designed to help you make your healthcare and HIV treatment decisions. Contact NAM to find out more and order your copies.

■ 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 'HIV in 2006: *the future now*', and will be held on 30th January 2006. For more details, go to www.aidsmap.com/forums.

■ www.aidsmap.com

Visit our website for the latest news about HIV & AIDS and a fully searchable treatments database and a complete list of HIV treatment centres in the UK.

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■ i-Base Treatment Phonenumber

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0808 8006 013

Mon-Wed, 12pm-4pm



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venue

3rd floor, Rooms 3C & D,
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Malet Street WC1 7HY

dates for your diary

■ January 30th 2006

7pm-9pm:

*HIV in 2006:
the future now*

Dr Mike Youle
Royal Free Hospital,
London

■ February 27th 2006

7pm-9pm

*Feedback from the
International
conference on
retrovirals and
opportunistic infection*

Keith Alcorn
NAM

■ March 27th 2006

7pm-9pm

Disclosure

Lisa Power,
Terrence Higgins Trust

If you would like further information about any of NAM's resources, please call us on +44 (0) 20 7840 0050 or email info@nam.org.uk

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