

aids treatment update

new HIV treatment guidelines – the flight from early intervention

In the middle of the 1990s when the trend in HIV medicine was to move away from treatment with single drugs and towards the use of combinations, plans for a large, international trial called Tempo were drawn up. Tempo would follow in the path of the Concorde study, a pivotal trial which found that using AZT earlier in the course of disease was no more effective than taking it later when the immune system had sustained greater damage. Tempo, which would have compared immediate versus deferred combination therapy, never got off the ground. There's been no further plan for this kind of when-to-start strategy trial since, in part due to practical barriers such as the likely low clinical event rate, but also because the view – not least from HIV treatment advocates – that such a trial would be unethical, has been voiced so loudly.

In comparison, few have questioned the ethics of *not* doing a trial of this kind. In both the UK and USA, new recommendations on how to use treatments for HIV infection have now adopted a more cautionary approach to the question of when it's best to intervene with anti-HIV drugs. It's easy to be wise after the event – and to gloss over the challenges a modern-day Concorde study would face. Without one, we'll continue to respond to this fundamental question with guesswork rather than anything more dependable.

Our annual reader survey accompanies this issue, if you have a free subscription. This is our best opportunity to hear from you about what you do and don't like about this newsletter, and how we might improve it for you. Please take a few minutes to fill it in and return it – you don't need a stamp.

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starting later

2 HIV experts say defer treatment – but what if you're already taking it? by anna poppa

New guidelines on how to use anti-HIV treatments have recently become available from the UK's professional body for HIV doctors, the British HIV Association (BHIVA). This year's revision has come out at around the same time as the publication of guidelines in the United States from the Department of Health and Human Services (DHHS), often referred to as the US federal guidelines.

Historically, doctors over here in the UK have always advocated a more conservative approach to treating HIV than those on the other side of the Atlantic. So while the American federal guidelines have previously advised that treatment be considered at CD4 counts of 500, BHIVA have settled on levels much lower than this – last year's UK guidelines suggested 350 was the appropriate point for treatment to begin.

This year both camps have taken a cooler, more pragmatic approach, advising that treatment can be delayed substantially. The US guidelines now say treat before the CD4 drops below 350, while BHIVA have gone for a cut-off of 200.

It's easy to misrepresent these two rather lengthy documents by reducing them to a series of sound bites. In fact, BHIVA suggest that some people would be advised to start earlier than others, for instance people with recurrent severe illness, or where the CD4 count is falling quickly or the viral load is high – both these situations are likely to result in more rapid progression of disease over the near term if there's no intervention. And BHIVA only strongly advise against treatment at CD4 counts above 350; meaning that any count

within the 200 to 350 zone would merit consideration of the risks and benefits of starting treatment.

However, the change towards later treatment is not mere fine-tuning. Most people with HIV who do not take anti-HIV therapy lose CD4 cells at a rate of around sixty a year. At this pace, the difference between a count of 350 and 200 is about two and a half years.

Debating the 'When to start' question is not an academic exercise, nor one that is only relevant to people who have yet to start themselves; it raises fundamental issues about the use and effectiveness of anti-HIV treatment which will clearly be pertinent to people who are taking treatment already. So what's behind this move to defer treatment, and what evidence is BHIVA's advice based on?

Understanding the move to defer

In HIV medicine, as in most things, context is everything. Previous guidelines were devised in happier circumstances. When protease inhibitors became available in 1996, optimism was the obvious response to the emptying of hospital wards. Another new development, viral load testing, demonstrated the profound effect this new approach to treatment had even on people who'd never needed a stay in hospital. Amidst seductive talk of using combination therapy not just to prevent AIDS but to *eradicate* HIV, antiretroviral treatment was re-branded as Highly Active.

There was no rigorous evidence that starting treatment before developing symptoms or having a CD4 count below the 200 mark would definitely extend life and put off opportunistic infections, but by 1996/97 few people were willing to justify exposing people with HIV to these risks in the name of 'good science'. And the theoretical case in favour of early therapy was robust: viral load was driving the loss of immune capacity which placed individuals at risk of progressively severe illness. Evidence from trials showed that HAART reduced viral load to levels so low that tests were unable to detect it. So long as people stayed on treatment, this state could be maintained for long, presumably indefinite periods.

Chinks in HAART's armour were appearing as early as 1997 when Peter Ruane, a doctor in a Los Angeles medical practice presented a case series of three men at a medical conference who had "striking atypical accumulations of fatty tissue in a pattern reminiscent of a 'buffalo hump', shortly after initiating triple combination therapy with protease inhibitors". People with HIV themselves had been discussing the problem on email lists all summer long.

Outside the clinical trial setting, the fallibility of these new treatments was showing up in other ways. The high success rates with regard to viral load suppression were not being duplicated in clinics. Drug regimens were complicated, and vulnerable to failure if they weren't followed strictly. Once an initial combination had failed, subsequent attempts at HIV control were generally less successful and seemed to require more drugs, in turn adding more complexity and greater risk of toxicity. In those countries and clinics where HIV drugs had been prescribed most aggressively, people who had never been at risk of opportunistic infections were dealing with stigmatising side-effects, while peering into an HIV drug pipeline which seemed to offer few viable options for later when their immune systems would need the support of effective treatment.

If there continued to be no data from trials set up to compare early versus late treatment, there was a gathering body of information from cohort studies – huge databases tracking thousands of people who'd started treatment. Assessing the incidence of death and disease according to the CD4 count when treatment was started, one cohort after another found little difference in risk so long as you started before the CD4 count fell below 200.

In fact these cohort studies are no more able to answer the question of when is the *best* time to begin than the early presentations showing tumbling viral loads, or the impression from clinical practice of intolerance to treatment. What each new piece of information does – and clearly the picture is very much more complicated than I am presenting in this broad overview – is alter the balance of risks and

benefits which every individual must figure into their own decision about when to start.

What is influencing BHIVA's stance?

BHIVA's recommendations on the timing of treatment differ according to disease stage. People who have been infected within the last six months (known as primary infection), may be in a unique position to benefit from treatment which could be lost as time, and HIV infection, progresses. But because there is no evidence of the long-term effect of intervening at this stage, BHIVA say people in this situation should consider treatment rather than strongly advising it be taken, and that if treatment is begun it should be within a clinical trial, (see UK trials review later in this issue). Some doctors may take a stronger view about the use of treatment in people who experience symptoms in primary infection, because this predicts a faster rate of disease progression.

In established, or chronic infection, the evidence in favour of the benefits of treatment is most clear for people who have symptoms related to HIV disease, and those who have low CD4 counts, meaning below 200. It follows then that BHIVA recommend that everyone with symptoms of HIV infection and a CD4 count consistently below 200, or who has been diagnosed with AIDS, or a severe or recurring HIV-related illness, should start treatment. Each of these circumstances present a high risk of further opportunistic infections which although treatable, may cause irreversible damage to health, or be life-threatening.

The research evidence which informs decisions about when people with established infection, but less immune damage should start treatment is relatively weak and presents some conflicting messages. A good deal of this research comes from observational cohort studies rather than from prospective clinical trials that were specifically designed to answer questions about the timing of treatment. (The limitations of this type of evidence were discussed in last month's *ATU* by Caroline Sabin). One of the key limitations of the cohort information in this context is that the available follow-up is relatively short, and when we are considering the timing of treatment, it is the

glossary

antiretroviral A substance that acts against retroviruses such as HIV.

CD4 A molecule on the surface of some cells onto which HIV can bind. The CD4 cell count roughly reflects the state of the immune system.

clinical trial A research study with people, usually to find out how well a new drug or treatment works and how safe it is.

HAART Highly Active Antiretroviral Therapy, a term used to describe anti-HIV combination therapy with three or more drugs.

immune system The body's mechanisms for fighting infections and eradicating dysfunctional cells.

opportunistic infections Specific infections which cause disease in someone with a damaged immune system.

protease inhibitors Family of antiretrovirals that includes indinavir, saquinavir, ritonavir, nelfinavir.

regimen A drug or treatment combination and the way it is taken.

toxicity The extent or ways in which a drug is poisonous to the body.

viral load Measurement of the amount of virus in a sample. HIV viral load indicates the extent to which HIV is reproducing in the body.

starting later continued

benefits and risks over the longer-term which are crucial, particularly the further one is from risk of HIV-related infections. In other words, it will always be more difficult to establish a benefit of very early treatment over later treatment, because it takes longer to evaluate the effects of the early treatment strategy.

BHIVA's view of the evidence we do have today is summarised below:

- Recent cohort data suggest that people who start treatment when their CD4 count is below 200 face a greater risk of death in the short-term than those who start while their CD4 is above 200.
- Most studies suggest there seems to be no difference in the short-term risk in people who begin treatment at different CD4 counts above the 200 level. One cohort disagreed with the others, finding that the risk of future illness *was* lower in people who began with a CD4 count above 350, but according to BHIVA, there is little other information to support starting treatment at this CD4 level.
- People who begin treatment when their CD4 count is below 200 may still have a similar CD4 and viral load response to those who start earlier.

BHIVA recommend that ideally, people should start treatment before their CD4 count falls below 200. Some people may start sooner than this, particularly those whose CD4 count is falling by more than 80 cells per year, because this is likely to mean that the count will fall below 200 within the near future.

Previous BHIVA guidelines have placed much more emphasis on viral load levels, an

indication of the activity of HIV within the body, as the marker for governing who should be treated and who could afford to wait. This year the role of the CD4 count, a marker of the immune system's health, is dominant. However, because people with a high viral load lose CD4 cells more quickly than others, and are at greater risk of illness or death in the short-term, they too may choose to start treatment sooner than others. Because cohort studies have not found that viral load provided additional useful information about response to therapy and future disease risk over and above that supplied by the CD4 count, BHIVA's emphasis is perfectly clear: "It should be the absolute CD4 count which drives decisions about when to start".

Delaying therapy reduces the impact of long-term side-effects and the development of drug resistance. It's also feasible, though not guaranteed, that waiting to start will mean that the treatment choices you are presented with will include drugs which are easier to take, less toxic, and perhaps more effective against HIV. Whilst this is clearly a hope rather than a fact, it seems a reasonable premise. Later therapies, new formulations and the practice of pharmacological enhancement (using drug interactions to boost the effects of drugs), have already provided a generation of treatments which are less onerous to take on a day-to-day basis. That today's drugs are safer is not yet clear, because they've not been in use for long.

Despite these recommendations, taking treatment remains an individual choice and some will choose not to start despite being advised to. These people are urged to review their decision regularly, and have their CD4 count and viral load monitored more frequently than usually recommended, for example every two months, so that changes can be recognised more quickly.

Views from UK treatment centres

We asked members of our Medical Advisory Panel how these changes fit with their current concerns and practice.

Professor Tony Pinching of St Bart's and the Royal London Hospital said, "Starting only

when CD4 is around 200 does risk sailing too close to the wind, since we know that people can get quite ill and even have AIDS-defining illnesses well above 200. Patients who are ambivalent about treatment anyway may now be inclined to wait too long and jeopardise their health”.

Dr Ray Brettle of Western General Hospital, Edinburgh, said, “The annual risk of death for an individual with HIV in Edinburgh is 1% maximum. The risk of AIDS is perhaps between 5 and 15%, yet the six to twelve month risk of having to stop an antiviral drug because of a side-effect is 20-35%. It’s not surprising this risk puts off individuals who are well or have only minor clinical disease. I have no doubt that if we had therapy that was safe in the long-term then probably the earlier the better, and certainly before the CD4 is below 200.”

Implications for stopping treatment?

Inevitably this move towards later treatment will raise the difficult question of whether people who started treatment at disease stages in which treatment would not now be advised, may consider stopping. BHIVA recommend that ‘structured treatment interruptions’ should not be seen as standard of care, and shouldn’t be undertaken outside a clinical trial. Most people who stop treatment get a rapid rise in viral load and a fall in their CD4 count. The immediate consequence of this will depend on the absolute levels, and so risks must be judged on an individual basis, (see *ATU* issue 104 for more on this).

Given that the stance on early intervention has

been more aggressive in the US, this issue could have greater pertinence over there. The US guidelines say, “As recommendations evolve, patients who have begun HAART at CD4 counts above 350 may wish to discontinue treatment. There are no clinical data addressing whether or not this should be done or can be accomplished safely.”

These data are being gathered though, including through the TILT study, which is currently recruiting in the UK (see sidebar). But in the meantime, Dr Martin Fisher of the Royal Sussex County Hospital, Brighton, offers this perspective; “Data on discontinuation suggest those most at risk of significant CD4 drop or clinical progression are those who started treatment with a low CD4 and *not* those who started with a CD4 count above the current threshold – certainly above 350.”

“The decision facing somebody who is tolerating their current regimen well may be quite different to somebody who is experiencing difficulties. If treatment is failing and the individual started therapy at a high CD4 count, then discontinuation could be considered as another alternative within the usual switch or stick debate. This may allow future treatment options to be saved, rather than used up when that person may be at little risk of HIV-related illness in the short to medium term.”

Martin continues, “Ultimately, these decisions are all about individualisation, and an open discussion between the person with HIV, their peers and their health care team.”

key conclusions

- New guidelines on the use of anti-HIV drugs have been issued in the UK and USA.
- Both advise that treatment should begin later than was previously recommended.
- The UK guidelines place stronger emphasis on the CD4 count to govern decisions about when to start than the viral load.
- The best time to begin anti-HIV treatment has not been established by research, and will continue to be a matter of opinion for the foreseeable future.
- Concerns about the risks and benefits of using HIV treatments have implications for those already taking the drugs as well as those who have yet to start.

TILT study

TILT is investigating the effects of continuing treatment versus interrupting it in people whose CD4 count is over 300 and whose viral load is controlled. Some of those who stop treatment will receive IL-2, an immune therapy. Anti-HIV treatment is re-started before the CD4 count falls below 200, and according to the trial’s treatment interruption protocol. TILT is recruiting at the Mortimer Market Centre and Royal Free Hospital, London, and the Royal Sussex County Hospital, Brighton. More information on aidsmap.com.

further reading

The BHIVA treatment guidelines can be read online at the NAM/ BHIVA website <http://www.aidsmap.com>. They will also be available in print in a forthcoming issue of the medical journal, *HIV Medicine*. The US DHHS guidelines can be found at <http://www.hivatis.org>



staying stopped

6 which interventions designed for people who want to stop smoking are most effective? by anna poppa

The occurrence of increased levels of fats in the blood in people taking anti-HIV treatments has had profound effects on the management of HIV infection. Raised blood fats, or 'lipids', is one element which forms part of the lipodystrophy syndrome.

Having high levels of a blood fat called cholesterol is one of four major risk factors for coronary heart disease. The others are smoking, having high blood pressure and being physically inactive, and the more risk factors you have, the higher your risk. Recent revisions to the BHIVA Guidelines, the UK's recommendations on how best to use anti-HIV treatment, say that people with raised cholesterol levels should be advised to stop smoking.

Of course, everyone who smokes can derive significant health benefits from stopping – four of every five lung cancer deaths are caused by smoking, and as we report in this month's *News in Brief*, the incidence of lung cancer may

be higher amongst people with HIV than in the general population. Smoking is also associated with cancer of the tongue, mouth, throat, bladder, kidneys, cervix, oesophagus, stomach and small intestine, and can cause chronic bronchitis and emphysema.

What works?

Last year the *British Medical Journal* published a systematic review of the evidence about the effectiveness of the range of interventions which are available to people who want to stop smoking. The review considered randomised controlled trials which followed participants for at least six months after they quit. Guidance from BHIVA is likely to be important; the review found that even brief advice from doctors helped smokers to quit.

Organisations such as Quit (see sidebar), can provide help to people who want to stop smoking. All advise that the interventions on offer can only help people who are motivated to stop. Whilst they can help ease nicotine withdrawal and lessen the urge to smoke, they cannot make you want to stop if you haven't already reached that decision yourself.

Psychological interventions

Both individual counseling and group therapy have been proven to help people stop smoking. Given that a group approach may be more cost-effective for health services, it may be that some HIV treatment centres will be persuaded to offer this type of help in future.

In the trials reviewed, therapists were usually clinical psychologists. However there was no evidence that one theoretical model was more effective than another in helping smokers to quit, (see sidebar). Twenty-four small trials investigated the effects of aversion therapy – where smoking is associated with something unpleasant – and this was not found to be effective. Self-help materials may be of little use if they are not given as adjuncts to support personal advice or counseling.

Nicotine replacement therapy

Nicotine is the addictive substance in cigarettes. Nicotine replacement therapy (NRT) aims to help people stop smoking by

weaning them off nicotine, lessening the withdrawal symptoms and cravings which many people experience when they stop. NRT comes in several forms: chewing gum, skin patches, nasal sprays, inhalers, tablets and lozenges.

The evidence from over ninety trials shows that NRT increases people's chances of stopping smoking by one and half to two times, regardless of whether additional forms of support are taken up at the same time. People who have taken part in NRT trials have tended to have some evidence of nicotine dependence and so it's less clear whether NRT has a useful role to play in helping less dependent smokers to quit. If you are the type of smoker who has a cigarette in the morning soon after waking, you are more likely to benefit from NRT.

There is little evidence that one type of NRT product is more effective than another and so individual preference is likely to be the most important factor. Skin patches provide a steady level of nicotine throughout the day, whereas other methods such the nasal spray gives faster delivery for when cravings are particularly bad. Some people use a combination of products, but this has been less well studied.

Patches come in three dose strengths, so that users can work their way down if they prefer, starting with the highest dose if you are a heavier smoker. If you choose patches, it will be just as effective to wear them while awake, rather than for the full twenty-four hours, and an eight week course should be expected to work just as well as wearing them for longer.

Patches may cause skin irritation and nausea, particularly when first used, and the gum, inhaler, spray and lozenges can all cause irritation in the mouth or nose. There is no evidence that NRT causes interactions with anti-HIV drugs. All forms of NRT are available on prescription, and several are available over-the-counter at pharmacies.

Drug therapy

Bupropion (*Zyban*) is a drug which has been licensed for use as an aid to quitting smoking. It's taken as a two month course of treatment, beginning one week before you actually stop

smoking cigarettes. *Zyban* can cause side-effects, such as insomnia, dry mouth, headache and fits. It also has antidepressant activity. In addition, it interacts with anti-HIV drugs, namely with protease inhibitors and NNRTIs, possibly requiring a dose alteration. It should not be taken with ritonavir, though it's unclear if this applies when a small dose is used to boost another protease inhibitor. So, depending on your anti-HIV regimen, your HIV doctor may be happier for you to try NRT or other forms of smoking cessation help first. Because *Zyban* can cause fits (seizures), it should not be prescribed to anyone at risk of fitting.

Other methods

According to the *BMJ* review there is no evidence that acupuncture, hypnotherapy or exercise help people to stop smoking.

Staying stopped

Seventy to eighty per cent of people who stop smoking restart within six to twelve months, and so as well as finding methods to help people give up, researchers are evaluating interventions which maintain cessation. A recent publication in *Annals of Internal Medicine* found that prolonged treatment with *Zyban* for a one year period was more effective than the standard two month course followed by a placebo, in helping people stay cigarette-free. The benefit from *Zyban* was lost one year after treatment had stopped.

Key conclusions

- Advice from doctors and one-to-one and group counseling are helpful interventions for people who want to stop smoking.
- Self-help materials are no better than brief advice but may be more effective than doing nothing.
- All forms of nicotine replacement therapy are effective.
- The antidepressant drug bupropion is effective, but interacts with anti-HIV drugs.
- There is no evidence that aversion therapy, exercise, acupuncture or hypnotherapy are effective.

Quit

Quit is a UK charity which provides help to people who want to stop smoking. Quitline can be reached on 0800 002200, or visit Quit online at <http://www.quit.org.uk>

support in Scotland

The Health Education Board for Scotland offer advice on smoking cessation at <http://www.hebs.com/topics/smoking/index.htm>. A telephone service, Smokeline, is on 0800 848484.

group for gay men

Gay Men Fighting AIDS (GMFA) are offering smoking cessation courses, in London, to gay men. Details from James on 020 7738 3712.

psychological models

Prochaska and DiClemente have published work on the psychological processes involved in addiction. See *Addictive Behaviours* 1985;10(4):395-406 and *Health Psychology* 1993;12(5):399-405.

references

Cochrane Review in *BMJ* 2000;321:355-358.
Bupropion for relapse prevention in *Ann Intern Med* 2001;135:423-433.



new trials open

8 a brief guide to clinical trials which have recently begun enrolling in the UK by michael carter

Genetics and side-effects

A trial at the University of Liverpool is investigating the role of genetics in the development of side-effects; specifically lipodystrophy, and hypersensitivity to co-trimoxazole (*Septin*). People with HIV are eligible if they have had a rash or fever while taking co-trimoxazole, *or* if they have lipodystrophy. Participants give a one-off blood sample which is submitted for laboratory analysis.

For every person entered into this study, his/her doctor is asked to enter a control patient who has either taken co-trimoxazole but did not develop a hypersensitivity reaction, or who has been on antiretroviral treatment but has not developed lipodystrophy, as appropriate. For information on eligibility, your doctor should contact the Medical Research Council Clinical Trials Unit on 020 7670 4783.

PI treatment after *Kaletra*

Abbott Laboratories is sponsoring two studies across the UK to evaluate the effectiveness of two new combinations of HIV medications in people who have not been able to achieve a viral load below 50 copies on an anti-HIV treatment regimen based on the protease inhibitor *Kaletra* (lopinavir/ritonavir).

People enrolling in the study will be given a combination of amprenavir/ritonavir or saquinavir/ritonavir, plus two nucleoside analogue drugs.

The first study, protocol number M00-261 is for people who have had *two* protease inhibitor-based regimens, the second including *Kaletra*, but have not seen their viral load fall, and remain, below 50 copies. Based on an initial screening, which will include a genotypic and phenotypic test for protease inhibitor resistance, participants will be allocated by their doctor to the most suitable of four treatment arms. Treatment will involve two nucleoside analogues, plus one of the following dual protease inhibitor combinations, each of which are to be taken every twelve hours:

- 750mg amprenavir plus 300mg ritonavir
- 1200mg amprenavir plus 200mg ritonavir
- 400mg saquinavir plus 400mg ritonavir
- 800mg saquinavir plus 200mg ritonavir.

The second study, protocol number M00-287 is for people whose *first* protease inhibitor regimen, based on *Kaletra*, has failed to suppress their viral load to below 50 copies. Participants will also be tested for protease inhibitor resistance by genotypic test, and divided into one of the four arms detailed above, or, if appropriate, a fifth arm where they will also receive the NNRTI, efavirenz. As above, participants will also receive two nucleoside analogues.

Both trials will last 48 weeks and will involve visits to the clinic at weeks two, four, eight, 12, 16, 20, 24, 32, 40 and 48. During each visit,

blood samples will be taken and other tests may be performed. Pregnant women and breast-feeding mothers are excluded from the study. This trial is enrolling at sites 1, 2, 3, 4, 6, 7, and 9, (see sidebar).

Tetra: four drugs at low CD4 counts

Tetra is an open label, single arm study looking at *Trizivir* (a combined pill including three nucleoside analogues; abacavir, AZT and 3TC), plus efavirenz, in people who are new to anti-HIV treatment, and have a CD4 count below 200. The study will evaluate the virological response over 48 weeks, plus adherence, safety and tolerability. Tetra is recruiting at sites 9 and 10.

DPC 083: a new NNRTI

Designed to evaluate the safety and effectiveness of the investigational NNRTI, DPC 083, this trial is being conducted on a double blind, placebo-controlled basis, and is divided into four treatment arms. Participants in each of the four arms will receive *Combivir* (AZT and 3TC) and either 50 or 100mg of DPC 083, or efavirenz. A placebo will replace the NNRTI you are not taking. Neither people enrolled on the trial nor their doctor will know which NNRTI they are taking and if they are taking DPC 083, which dose they are receiving.

The trial will also be used to see how effective an antihistamine is in preventing the rash which can affect people who take NNRTIs, and so some trial participants will also be given a single antihistamine pill daily for the first 28 days of the trial.

The trial involves visits to the clinic at four weekly intervals for 48 weeks where blood samples will be taken. To be eligible you must be 18 or over and never have taken anti-HIV drugs before. Pregnant women and breast-feeding mothers are excluded. Recruiting at trial sites 5 and 9.

Nelfinavir long-term safety study

This is a long-term trial looking at the safety and effectiveness of treatment with the protease inhibitor nelfinavir and two nucleoside analogues. In particular, it will seek to

establish the safety and effectiveness of twice daily dosing of nelfinavir, and the effects of nelfinavir on body fat changes (lipodystrophy). There are also three sub-studies, one of which *all* trial participants will be asked to join, which will be examining blood levels of nelfinavir. These will be measured three, six, twelve and twenty-four hours after taking the drug. Each of these sub-studies will involve a short stay in hospital. An additional, voluntary sub-study test will evaluate genotypic resistance to nelfinavir.

The trial will last for 96 weeks and will involve regular 12 weekly clinic visits when fasting blood samples will be taken. To be eligible you must have been on twice daily nelfinavir for at least 72 weeks and have a viral load below 50 copies. This study is enrolling at trial sites 3, 5, 8, and 9.

Newly infected with HIV?

St Mary's Hospital in London is looking for people who have been recently diagnosed as HIV-positive, but who had a negative test in the six months prior to their diagnosis – that is, they are recently infected with HIV. A trial is underway to see if a short course of treatment (three months) with *Combivir* and nevirapine helps prevent damage to the immune system in the period immediately following infection with HIV. Recently infected people who do not wish to take treatments are also asked to enroll in the study so that their health can be tracked for comparison purposes. Pregnant women and nursing mothers are excluded.

See aidsmap: many more trials listed

Trials noted in this article have begun recruitment relatively recently. Remember that several others are ongoing and are enrolling participants at centres around the country.

These include the Medical Research Council trials *Esprit*, which is investigating the effect of the immune therapy IL-2 in people taking anti-HIV treatment, and *Optima*, which compares different treatment strategies in people whose anti-HIV treatment has failed. More details are available by selecting *Take me to... Clinical trials* on NAM's website aidsmap.com.

trial sites key

- 1 Royal Sussex County Hospital, Brighton, 01273 664 532
- 2 Western General Hospital, Edinburgh, 0131 536 6220
- 3 Chelsea and Westminster Hospital, London 020 7846 6161
- 4 St George's Hospital, London 020 8725 3355
- 5 King's College Hospital, London 020 7346 3479
- 6 St Mary's Hospital, London 020 7725 6790
- 7 St Thomas' Hospital, London, 020 7925 9292
- 8 Mortimer Market Centre, London 020 7380 9810
- 9 The Royal Free Hospital, London 020 7794 0500
- 10 North Manchester Hospital, Manchester 0161 720 2615



Will rise in sexually transmitted diseases affect HIV rates?

Experts from the Public Health Laboratory Service have warned that the recent rise in sexually transmitted infections in the UK may translate into an increase in new cases of HIV. The increase in the number of people having unprotected sex has already been implicated in the recent re-emergence of syphilis, (see *ATU* 103 and this month's *NAM Factsheet*), and research has suggested that many have become complacent about the need to maintain safer sexual practices since the introduction of antiretroviral therapies. The rise in new diagnoses of sexually transmitted infections has been particularly noticeable in young people and observers fear that any rise in new HIV infections may disproportionately affect young people.

The Government plans to run a health education campaign in early 2002 in an attempt to slow the rise in sexually transmitted infections. This campaign will be the first of its kind in over a decade, and forms part of the National Strategy on Sexual Health and HIV.

The total number of new diagnoses of HIV in the UK during 2000 has now reached 3,551. This is the highest annual total since recording began in the 1980s and may rise further as late reports are received.

Trial supports early detection and treatment of hep C

A German study published in the November 15 issue of the *Journal of the American Medical Association* has shown that treatment with interferon-alfa during acute (early) hepatitis C (HCV) infection can prevent the disease from developing to the chronic stage. Treatment once infection has become established (chronic phase) clears the virus in around 55% of patients.

Forty-four people who were suspected of having acquired HCV recently were given 5 million units of interferon-alfa subcutaneously, daily for four weeks and then thrice weekly for a further twenty weeks. In total, 42 of the 43 patients (98%) who completed the twenty four weeks of treatment and twenty four weeks of follow-up, had no detectable HCV viral load (RNA) at the end of the period of follow-up. Neither the genotype, route of HCV acquisition or gender of the patient affected the response to treatment. Only one patient stopped treatment due to side-effects.

Treatment in early infection may have several advantages. It may allow for the use of interferon monotherapy rather than interferon combined with ribavirin (dual therapy); monotherapy is often associated with less side-effects than dual therapy. Also, the treatment course may be shorter; twenty four weeks

instead of forty eight, (as is recommended for chronic HCV infection with genotype 1). The rate of HCV RNA undetectability of 98% is remarkable and compares to around 55% seen among chronically infected people treated with dual therapy. The authors recommend studying the use of pegylated interferon in acute infection as this requires once weekly rather than thrice weekly injections, and will help improve tolerability and reduce side-effects.

Non-AIDS cancers in people with HIV

A study recently published in the *American Journal of Epidemiology* compared rates of cancer between 122,993 AIDS patients in the State of New York and the general population of New York, in the pre-HAART era (1981-1994). This revealed that people with HIV are not only at greater risk of developing AIDS-defining cancers such as Kaposi's sarcoma and invasive cervical cancer but that people with advanced HIV are also significantly more likely to develop certain other cancers.

Whilst HIV-positive men are 100 times more likely to develop Kaposi's sarcoma than HIV-negative men, and HIV-positive women are 200 times more likely to develop Kaposi's sarcoma than HIV-negative women, the researchers also established that people with advanced HIV are three times more likely to develop other forms of cancer such as anal or skin cancer. The researchers were also able to identify which non HIV-related cancers gay men, heterosexually infected women and intravenous drug users were more likely to develop.

The US AIDS Cancer Match Registry identified higher rates of both testicular and lung cancer, and concluded that the higher rate of lung cancer was not confined to the most common smoking-related cancer of the lung, adenocarcinoma.

Researchers from the Chelsea and Westminster Hospital in London are gathering data from a cohort study on the incidence of cancer among people with HIV in the UK. Such data

collection has only recently begun in earnest, and very large numbers of people must be followed over long periods to provide reliable information on this question.

Tenofovir approved in Europe and US as second-line therapy

The European Union's Committee for Proprietary Medicinal Products (CPMP) has recommended marketing authorisation for Gilead Science's experimental nucleotide analogue tenofovir (*Viread*). The decision, announced as this newsletter went to press, means that tenofovir will become available on prescription in the UK early next year.

The US Antiviral Drugs Advisory Committee of the Food and Drugs Administration had approved the drug several week earlier. Both committees have given authorisation to tenofovir's use in people who have experienced virological failure on other anti-HIV drugs, rather than in people who are new to antiretroviral treatment.

Currently tenofovir is available in the UK through an expanded access scheme for people who cannot tolerate nucleoside analogues, or who are experiencing difficulties constructing a new regimen as a result of nucleoside analogue drug resistance. Tenofovir is taken as one tablet, once daily with food.

Dr Graeme Moyle at NAM forum on lipodystrophy: 26 Nov

Lipodystrophy is the subject of the next NAM forum on Monday, 26th November, when our guest speaker will be Dr Graeme Moyle of the Chelsea & Westminster Hospital. The forum will take place at the University of London Union, Malet Street, London WC1 from 7-9pm. Forums are free and everyone is welcome. A sign language interpreter will be present.



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any questions

For an introduction to HIV treatment issues
The booklets in NAM's Information Series for Positive People are free to people with HIV. This easy-to-read series covers six key topics: Viral Load, Clinical Trials, Nutrition, Anti-HIV Drugs, Resistance, and a Glossary.

The HIV & AIDS Treatments Directory
This 600 page book, published twice a year, is a comprehensive guide to the medical aspects of HIV. Available at only £12.95 to people with HIV, £64.95 to professionals.

<http://www.aidsmap.com>
NAM's resources are also available online at [aidsmap.com](http://www.aidsmap.com). These include our extensive and searchable treatments database, the latest news on treatment developments, our online directory of AIDS service organisations, hundreds of links to recommended HIV-related sites, and free downloadable resources.

Monthly NAM information forums in London
Each month an expert speaker discusses a treatment-related topic. Entry is free. Future forums are advertised inside this newsletter.

AIDS Treatment Phonenumber 0845 9470 047
From Terrence Higgins Trust: Mon & Wed 3-9pm, Tue 3-6pm.

NAM recommends that you discuss all your treatment decisions with your doctor.



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