

# aids treatment update

## brian gazzard speaks to atu

This month's ATU falls into two distinct parts, with the first exploring the generalities of HIV prevention and treatment and the other a specific aspect of HIV treatments. The broad overview is provided by an interview with one of the UK's leading HIV physicians, and the specifics comes in the form of a detailed examination of therapeutic drug monitoring.

Brian Gazzard answers a diverse range of questions covering late diagnosis; US recommendations for six monthly HIV tests for gay men; whether there is a new wave of HIV infections amongst gay men in the UK; hepatitis C co-infection; side-effects; when to start therapy; and, the forthcoming Barcelona conference and the world-wide epidemic.

Therapeutic drug level monitoring is being used increasingly as a tool to monitor the effectiveness of anti-HIV therapy. However, research supporting its usefulness is limited and its most useful applications are unclear. The second article provides an examination of how anti-HIV drugs are absorbed by the body, why levels vary, and the current UK guidelines for the when to use drug level monitoring.

You may have noticed that for the past year or so the Factsheets accompanying ATU have been building into series. The current series provides brief introductions to the body's organs, with this month's Factsheet on the heart. Over the coming months many of NAM's catalogue of Factsheets will be revised with updated versions posted on our website, [aidsmap.com](http://aidsmap.com) and the titles to look out for will be mentioned in ATU.

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# brian gazzard

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**Anna Poppa (AP): According to the recent audit exercise undertaken by the British HIV Association (BHIVA), many of those in the UK who start HIV treatment late do so because they are diagnosed late. What can be done about this, and what should be BHIVA's role?**

Brian Gazzard (BG): It's clear from the BHIVA audit that perhaps a third of patients present at a time when their treatment is going to be sub-optimal because their CD4 count is less than 200. When you take these data in conjunction with those from the Middlesex group – that such patients have often come into contact with doctors several times in the preceding two or three years, often with very suggestive symptoms that they are HIV-infected – what is absolutely clear is that we are not encouraging HIV testing appropriately.

For the patients who don't realise that they are HIV-infected, there is a general education message to be communicated that HIV infection is a major risk for certain groups. There's also a need for a doctor-specific message that doctors are not taking the opportunity to test appropriately with risk groups, and that this is particularly unfortunate when there are symptoms which have highly suggestive of HIV infection.

I think there's a role for BHIVA, and a role for the Government's National Strategy on Sexual Health, to roll out testing much more widely. I think that HIV testing should be suggested in general practice, in general medical clinics and in surgical clinics, as well as just coming to the GUM clinic. So I think that there's a general

educational role there for BHIVA and also a political role to make sure that testing is on the agenda.

**AP: In the USA, the Centers for Disease Control have just recommended that gay men test for HIV every six months. Do you think we'll see a move like that here?**

BG: The issue is that it clearly depends on the risk that you're running. If you've been in a long-term monogamous relationship for twenty years then testing is not sensible. If you're not in that sort of situation then the risk is high.

There are two difficulties I think, really. One, there is a changing perception of what is safe in terms of HIV infection. So, five years ago oral sex was considered safe and therefore people didn't perceive themselves to be at risk from oral sex. Now it's quite clear that oral sex can transmit HIV; what isn't clear is how common that is. I am struck by the large number of people I am seeing who tell me that their only risk factor was oral sex. You don't know if the risk factor would have been a hundred times more if they'd all been having anal sex, or whether oral sex is a good bit riskier than was previously thought. Now that's part of the perceptual difficulty for HIV testing. Many people wouldn't regard themselves as 'at risk' if all they were having was oral sex. I think that message is a very complex issue for some people, because if you say oral sex is unsafe as well then they may well think 'there's nothing I can do so I might as well do everything'.

The other difficult issue related to perceived

risk is that risk is ethnically related. Certain people are at considerable risk from where they are born. Having sex in Botswana is clearly more dangerous than having sex in Brighton. That's a reality, but how you translate that into a sensitive message that ensures that the people who are HIV-positive might actually be tested is quite complicated.

**AP: Following the rise in syphilis cases in the UK in the last year, there's been a lot of talk about a new wave of HIV infections amongst gay men. Are you seeing this at the Chelsea and Westminster?**

BG: No. I think that the outbreak of syphilis is a major problem, [but it is] likely driven primarily by sexual behaviours which have been thought of as relatively safe in terms of HIV. It's quite clear that syphilis is a great deal easier to contract than HIV. It's pretty unpleasant to have syphilis but I don't think it's going to translate into a new wave of young gay men with HIV. This is the biggest clinic in the country and I don't perceive that to be true. I think that there are sentinel signs of worry, but I don't see it being translated into a great new epidemic.

**AP: And what about hepatitis C infection? Do you screen your HIV patients here?**

BG: Yes, we screen all our patients for hepatitis C and have done for four or five years now. I think that what we should be thinking of moving towards is screening everybody with PCR [which detects hepatitis C viral load] because some of the people who were originally antibody positive and PCR negative seem to become PCR positive again, and a few people, anecdotally, are PCR positive without hepatitis C antibodies. So at the moment we're not screening everyone with PCR, just people with perceived risk and abnormal liver function.

Hepatitis C is very difficult for two issues. One is NICE [the National Institute for Clinical Excellence, a government body which rules on the provision of new medicines by the NHS]. They have yet to say if we can use peg-interferon and ribavirin, and the dataset for HIV-positive patients is small compared to that

for HIV-negative patients (though the data that exist do suggest the results are very similar). [See *ATU* issue 113].

Second is that I think there are likely to be dramatic improvements in the treatment of hepatitis C. At the moment the view in the US is that virtually everybody who is hepatitis C PCR positive should be treated. I'm still worried that this is a very tough regimen for patients, many of whom are at no risk of dying, and a very small risk of transmitting it to their partners. There may be treatment which is much better for them around the corner in two or three years time, and it is possible that present treatment may make future, more effective treatment more difficult to give. So it might be a situation like the one that existed right back at the start of HIV, when knowing what we know now you'd have been better off not taking AZT monotherapy and waiting for better treatment. Is the same going to be true for hepatitis C? I don't know the answer, but I'm relatively cautious.

I think perhaps people who have had hepatitis C for a significant period should have a liver biopsy to see if they need treatment. Non-1 genotype should be treated if needed as the chances of cure are very high, but for genotype 1a and 1b, which are the most common here in the UK, rushing into treatment now is not the right answer.

**AP: One of the things I was struck by at the recent Seattle Retroviruses Conference was the proportion of 'late breaker' presentations which focussed on antiretroviral side-effects. This shows how the issue has come centre-stage. What's been the impact of lipodystrophy on clinical practice here at the Chelsea and Westminster?**

BG: For at least three or four years, I felt that the stigmatising effects of lipoatrophy [fat loss] particularly were such an important issue for patients that PIs [protease inhibitors] were no longer the first choice regimen. All the data we have at the moment is that NNRTI-containing regimens are equally potent as PIs, but that the side-effect profile of PIs made

**glossary**

A booklet of medical terms, *Glossary*, used to discuss HIV & AIDS is available from NAM. Copies are free to people with HIV. Telephone 020 7627 3200 or email [info@nam.org.uk](mailto:info@nam.org.uk).

## brian gazzard continued

them second rather than first-line therapy. I believe that to be true at all levels of disease, whether you have KS or whatever.

I've been careful to say that I think it's the lipoatrophy that's important because it's stigmatising. I remain a little bemused about the lipid [blood fat] abnormalities and whether they really are atherogenic [likely to result in heart disease] or not. I was very impressed by the Sam Bozette data in Seattle which showed that there was a considerable short-term reduction in cardio-vascular mortality [in people taking antiretrovirals; see *News in Brief ATU* issue 112] which fits with the current data and theories about infection being very important in atheroma, and therefore a lot of this is related to the immunological effects of a chronic infection, as well as our diet and a lot of other things.

The risk benefit analysis for people with HIV with a CD4 count of around 200 is absolutely straight forward, one in two of them will die in the next few years if you don't treat them with antiretrovirals. Even in the highest risk group of older, male smokers, the coronary artery event rate is low compared to the benefits you'd get from treating with HAART.

It isn't that you shouldn't use antiretrovirals, it's that you should use them cautiously. I don't think that two NRTIs and an NNRTI never causes lipoatrophy, but there's ample data to say it is less likely to. It may be that the next PIs, for example atazanavir, may be free of lipodystrophy, and that may change one's perception of first versus second line treatment for that particular drug.

### **AP: And what about your use of NRTIs?**

BG: They are in a different category. There is a paper in this month's *AIDS* produced by

researchers here that shows that lactic acidosis [a side-effect of NRTIs] remains a very rare phenomenon. There is no doubt that PIs and NRTIs act synergistically in terms of lipodystrophy but I think that the data so far say that NRTI regimens are less effective in treating HIV. So you might be trading off a very rare NRTI toxicity for a less effective treatment. I think it's a historical accident that we are using NRTIs in all regimens but the limited data so far suggests that they're important in those regimens.

### **AP: There'll be no revision to the BHIVA guidelines until later in 2002. We know the UK guidelines are influential abroad; what sort of changes do you expect this time?**

BG: My personal view as just one of a large number of people who write them is that we need to be a bit more prescriptive. I think that goes for what I've said about first-line NNRTIs versus PIs. The 2NN data [from a trial comparing efavirenz and nevirapine-containing regimens in first-line therapy] should inform us of which NNRTI we might want to use first-line pretty soon. There are issues about the use of tenofovir in salvage because tenofovir is a very expensive drug and it's going to be a major issue for purchasers.

So I don't see a big change but I think we need to be a bit more pragmatic, and that we should get off the fence about the unimportance of viral load in making a choice about when to start treatment. I think we should get off the fence about what the optimum starting therapy is and about what the preferred PI regimens are, and we need to factor in more clearly when we'd use tenofovir.

### **AP: The UK's Medical Research Council has been conducting a feasibility exercise over doing another when to start trial. Clearly**

**many people don't support that type of study, and yet it's a fundamental issue for those considering HIV therapy. How long do you think the HIV community can go on avoiding this question?**

BG: The problem with a when to start study is really that everybody has to share the dilemma that it might be worth starting at 350 [CD4 cells] as opposed to 200. The difficulty is that we've got to show an improvement in the results, with less toxicity, at 350 which is going to be a very big hurdle.

I think the more interesting question is actually the SMART study [see *ATU* 110], which we are going to take part in. That study is looking at drug sparing versus drug use, so people with a particular CD4 count go on HIV therapy until the CD4 count drops below 250, versus changing every time the viral load becomes detectable. That's a way into doing a when to start trial. And it's also about what to monitor; your CD4 count or your viral load. What's very important, both for the developing world [and others] is if you don't need to monitor viral load, it might be easier to give antiretroviral treatment. If SMART were to show that CD4 count monitoring and changing at low CD4 counts was as good a policy as changing every time viral load becomes detectable, that would open up the possibility of other studies along the same lines.

I think the problem is that with the present drugs and risk benefit ratios, it's pretty clear that most people think that around 200 is the right time to start. It would be difficult, in the UK anyway, to get sufficient numbers of people to start at 350 or to be randomised to start then or wait til 200. They might have strong views either way, but to actually say 'I don't care' is a difficult issue.

**AP: The 14<sup>th</sup> International AIDS Conference starts in Barcelona next month. What are your expectations of the meeting?**

BG: I think Barcelona is a very important meeting because it brings together people who are caring for people with HIV from a broad spectrum of groups.

Normally it's not the best forum for major advances in therapeutics or pathogenesis. The 2NN study will be important regarding NNRTIs. There'll be further data about atazanavir and its potency, and I think there are data on mega-HAART versus 'mini-HAART' in late disease, which might influence how we practice medicine in this difficult group.

**AP: The last International AIDS Conference, in Durban two years ago, is considered to have been important in prompting change about global access to treatment. Do you think things have changed as quickly as people wanted?**

BG: No they haven't. [The Chelsea and Westminster] are heavily involved in a project in Botswana where the logistic difficulties and political difficulties are enormous. I think the cost-benefit analysis in the *Lancet* recently [Marseille et al, *Lancet* 25 May 2002] about how expensive it will be to provide antiretrovirals in the developing world was an important prompt to pause and consider what we are actually doing – is it possible?

In my view [improving access to HIV treatments] is a pilot for a much bigger project – can you rationally improve health care in Africa with the resources which we currently have available? A lot of the resources which are costed into antiretroviral care will improve people's health in a lot of other ways as well. HIV is important because it points the way with what could be done with quite modest resources, and modest desire to change the world for the better to improve a wide range of illnesses, not just HIV. Can we actually find a way of providing high technology treatments in a resource-poor setting? I believe the simple answer is yes, we have to try.

The project in Botswana is to help train the local people to do it appropriately themselves. So far it's been very successful, in that the training programmes are working very well, the doctors are getting confident in being able to do it, the drug supplies are arriving, and people are being treated. So that's a triumph really. I think that the difficulties are enormous but worth pursuing.

# testing drug levels

Therapeutic drug level monitoring is emerging as a more frequently used tool for managing anti-HIV therapy. Research supporting its use is limited at present and so the most suitable applications are unclear.

## How are drugs absorbed?

Once swallowed, anti-HIV drugs pass through the digestive system where they are absorbed into the blood-stream and distributed throughout the body. The rate at which they are absorbed varies between individuals. This means that if two people take identical treatment at the same doses and with the same foods, the amount of drug which will reach their blood-streams can be very different. In addition, drug levels vary within individuals, due to variations in food intake, interactions with other drugs taken, and the presence of infections.

To a certain degree, this variability is unimportant. In order to be effective against HIV, antiretrovirals must reach a level in the blood which falls within a range that is established when new drugs are first developed. A blood level which is higher than this 'therapeutic range' can lead to more side-effects. Conversely, a lower level will allow ongoing HIV replication, which provides the circumstances for drug resistance to develop, causing the treatment to fail.

Drug levels reach their peak soon after they are taken, and then taper off over the subsequent hours to a lower 'trough level' before the next dose. This trough level is important in determining a drug's efficacy. For example, early study of the NNRTI delavirdine found that the drug's activity followed a typical

dose-response curve. That is, at very low blood levels there is no anti-HIV activity at all, but above a certain trough level there is a rapid increase in activity.

High peak levels or high drug exposure with the following drugs are associated with side-effects:

- Ritonavir: raised triglycerides, circumoral paraesthesia (numbness around the mouth), diarrhoea.
- Indinavir: kidney stones, colic and other urinary tract/ kidney problems associated with the accumulation of indinavir crystals.
- Efavirenz: central nervous system side-effects, such as vivid dreams, anxiety, disorientation.

## Variability in PI levels

Amongst antiretrovirals, the greatest degree of variability in blood levels is seen with protease inhibitors (PIs). PIs are processed (metabolised) into inactive products relatively quickly. Their metabolism (and that of NNRTIs) is dependent on the liver, involving a 'pathway' called the cytochrome P450 system, which is responsible for processing many other drugs and nutrients. Interactions between these different substances can affect the speed at which they are metabolised, causing blood levels to rise or fall.

The activity of P450 is itself variable: some people are rapid P450 metabolisers and others are slow. These variations are influenced by genetic factors, some of which are known to be related to ethnicity, meaning that drug absorption can also be influenced by race.

There are gender differences in drug metabolism too. Women have been shown to metabolise saquinavir more slowly than men, resulting in 50% higher blood levels. This is possibly due to lower body weight, although there could be other mechanisms which are not yet fully understood.

### Poly-glycoprotein & other proteins

Poly-glycoprotein, or P-gp, is a protein found on the surface of cells in the gut, the blood brain barrier, kidneys, liver, and around one in ten CD4 cells (the immune cells which HIV targets). Dubbed the 'cellular vacuum cleaner', it flushes drugs out of cells and back into the gut. P-gp seems to affect levels of protease inhibitors found in cells. While some PI levels are lowered by P-gp, nelfinavir, saquinavir and ritonavir all inhibit P-gp. Drugs which induce P-gp (such as St John's wort), in turn lower intracellular levels of the protease inhibitors. P-gp also plays a role in preventing PIs from penetrating the brain and foetus, thus creating possible sanctuary sites where HIV can remain largely unchecked.

MRP is another protein which flushes protease inhibitors from cells. Both P-gp and MRP are expressed by T-cells. Expression is regulated by a particular gene, and there is evidence that white people are more likely to express P-gp than black Africans. Experts do not currently know whether HIV itself interferes with these proteins, but there is some evidence that P-gp plays a role in HIV binding and entry, and lower expression of P-gp has been observed amongst people with HIV.

PIs bind to a protein called alpha 1-acid glycoprotein (AAG). This 'protein binding' prevents them from acting against free virus in the plasma. People with high levels of AAG may therefore experience reduced antiviral effectiveness. AAG is raised in people with high viral load, in those with higher body weight, and in people of African origin.

### Measuring PI levels

Drug level monitoring generally involves a one-off blood sample taken in the morning, just before the first dose of the day is due, when the concentration of the drug in the blood will be

at its lowest. The earliest this test should be done is around two weeks after starting the drug, when blood levels should have stabilised.

People whose trough level is too low then have the option to modify their treatment, for example by continuing with their current combination and adding a small amount of ritonavir. Ritonavir inhibits the effects of both P450 and P-gp, and this is why its use in combination with other PIs raises the blood levels of the other drug.

An alternative application for drug level monitoring is to identify people who are absorbing drugs quickly and getting very high peak levels just after a dose, which may cause side-effects. In these circumstances there may be the option to split doses to iron out the peaks, or to reduce the dose altogether.

The Athena study, carried out in the Netherlands, found that therapeutic drug monitoring of nelfinavir and indinavir levels is valuable in people taking these drugs as part of a first-line HAART regimen. In nelfinavir recipients, after one year of follow-up, 81% of those who received therapeutic drug monitoring and dose adjustment (where necessary) had undetectable viral load, compared to 59% of those who did not receive drug level monitoring. People in the drug level monitoring arm received up to three drug level tests (because the effects of any dose adjustment were confirmed by further drug level assessment). After the first measurement, patients with low nelfinavir levels were reminded of the importance of taking nelfinavir with food, and in half the cases this resulted in improved nelfinavir drug levels on the next measurement. If blood levels were still sub-optimal after the second or third measurements, the nelfinavir dose was raised.

Athena also looked at people receiving indinavir as first-line therapy. Here access to drug level monitoring and subsequent dose adjustments produced a greater likelihood of achieving undetectable viral load after one year (75% versus 48%), and reduced the risk of needing to stop treatment permanently because of side-effects.

#### editor's note

This article summarises a more detailed review of therapeutic drug level monitoring written by Keith Alcorn, which is available online at [aidsmap.com](https://aidsmap.com). References for studies mentioned here can be found on [aidsmap](https://aidsmap.com).



## testing drug levels continued

The PharmAdapt study, on the other hand, showed no benefit from therapeutic drug level monitoring carried out four weeks after switching to a new protease inhibitor chosen on the basis of a genotypic resistance test. However, this study has a number of flaws which may not make it applicable to clinical practice. The study may have been too small to detect differences between the two arms. Also, the cut-off points at which dose adjustment might be necessary were derived from the drug levels necessary to inhibit wild-type virus (virus with no resistance mutations), not drug resistant virus. Finally, a four week delay between testing and dose modification in patients with drug resistance may not have been helpful, since this delay would have increased the risk that additional drug resistance mutations could develop.

### Drawbacks of drug level monitoring

A number of factors may distort the results of therapeutic drug monitoring, particularly in relation to PIs.

For example, levels of indinavir can vary during the menstrual cycle and as outlined above, levels of AAG can also influence PI levels. AAG levels rise during periods of infection, stress, and injury, all of which speed up the clearance of PIs from the blood. For this reason, it is recommended that drug level testing is avoided during any type of acute illness.

The usefulness of one-off testing to assess PI levels has been questioned by researchers who found that one trough sample did not correspond with drug concentrations established from repeated testing. Another study found that the body's daily cycle (diurnal rhythm) affects concentrations of nelfinavir, with higher trough levels seen in the morning compared to the evening.

Finally, even if drug levels appear to be optimal, they may not be adequate to inhibit virus with reduced sensitivity to a drug (drug resistant virus). If drug levels are just about adequate, this may result in effective inhibition in someone with wild-type virus, but may not prevent viral rebound in someone with virus that has reduced sensitivity to the drug.

### C<sub>min</sub> and antiviral activity

C<sub>min</sub> is the minimum concentration of a drug measured between one dose and the next, and it's become a focus of competition between the manufacturers of protease inhibitors, as they attempt to sell the merits of their products.

Pharmaceutical companies conduct test-tube studies which measure the concentration of a drug needed to inhibit viral replication by 50%, 90% or 95%. These values are known as the IC<sub>50</sub>, IC<sub>90</sub> and IC<sub>95</sub> (IC stands for inhibitory concentration). Generally IC values refer to the concentration required to inhibit wild-type virus. More drug is needed to inhibit resistant virus, so IC values get higher as virus becomes more resistant. This means that the IC value for one virus may be very different to the IC value for another.

### The inhibitory quotient: IQ

The ratio between the C<sub>min</sub> and the IC<sub>50</sub> gives a value called the inhibitory quotient (IQ). This value is a way of numerically illustrating the 'comfort zone' which exists when a particular drug is used. For example, if the trough level (C<sub>min</sub>) of a drug is 50 and the IC<sub>50</sub> of a drug is 10, the ratio will be five. In other words, the trough level is five times higher than the minimum concentration needed to inhibit 50% of virus replication. The IQ has been proposed as a way of predicting response to treatment, but further studies are needed to determine the usefulness of the IQ.

The GART study which evaluated switching therapy based on resistance testing and expert advice, found a significant relationship between the IQ twelve weeks after switching and viral load reduction at that point.

A modified IQ (dubbed the Virtual IQ), calculated using VIRCO's *Virtual Phenotype* resistance test, has also shown success in predicting response to treatment. A study of 37 people treated for 48 weeks, found the Virtual IQ a better predictor of success than either genotypic resistance testing or the *Virtual Phenotype*.

### Testing levels of other drugs

Therapeutic drug monitoring has largely focussed on PIs, partly because of large observed variations between individuals, but also because of the faster metabolism of PIs. However, several studies have called attention to the potential therapeutic implications of drug level tests for nucleoside analogues (NRTIs) and non-nucleosides (NNRTIs).

### Monitoring NRTI levels

Until recently it was very difficult to measure how well nucleoside analogues were penetrating into cells, and it was difficult to do large scale studies on the impact of variations in intracellular (within cell) levels on treatment response.

Nucleoside analogues, such as AZT or ddI, require an additional step in their metabolism (called phosphorylation) inside target cells in order to reach their active form. Measuring their concentration in plasma may not therefore provide an accurate reflection of intracellular levels of this active form.

The University of Liverpool HIV Pharmacology team have reported on the development of a new method for measuring NRTI levels, but this is not in routine use at present and requires further validation.

### Monitoring NNRTI levels

A test has also been developed to measure concentrations of nevirapine in saliva, which are about half the levels found in blood plasma. Researchers are investigating salivary drug

testing for other antiretrovirals, which would offer a cheap and easy testing method.

High levels of efavirenz have been associated with increased severity and frequency of central nervous system side-effects, while low levels are associated with higher rates of treatment failure. A second study reported contrary findings however, reporting no relationship between efavirenz peak levels or total exposure and the risk of developing central nervous system side-effects.

### The link with adherence

Aside from the biological factors which influence drug absorption discussed above, a central factor in ensuring that blood levels remain within the therapeutic range is treatment adherence (always remembering to take your pills on time and within any recommended food guidelines).

Generally, the use of drug level tests to monitor adherence is frowned upon, because it is expensive compared to other methods, can harm the relationship between patient and doctor, and reflects adherence levels only in the time period prior to the test.

### UK recommendations

At present, British treatment guidelines recommend drug level monitoring in people taking indinavir or nelfinavir, and in circumstances where doses other than those recommended by the manufacturer are being used. It is also recommended in cases of severe liver impairment (because the liver is instrumental in drug metabolism), and to manage side-effects. In patients with high peak levels but no current evidence of side-effects, dosage reduction may be a strategy to prevent their development.

Drug interactions such as between methadone and protease inhibitors, or between NNRTIs and protease inhibitors may also be grounds for recommending a test after starting treatment. Finally, monitoring drug levels in young children, especially below the age of two, may be useful due to the wide variability in the metabolism of protease inhibitors and NNRTIs among this age group.

### drug level testing at University of Liverpool

At present, the only UK laboratory which performs therapeutic drug level monitoring is the Department of Pharmacology and Therapeutics at the University of Liverpool. The cost is £40 per sample per drug (exclusive of transportation and handling costs). The group recommend that tests should ideally be performed on two samples: a trough level and a peak level. Tests are available for all currently licensed PIs and NNRTIs (plus delavirdine). A specialist service is available for testing AZT, ddI and ddC levels. (See <http://www.hiv-druginteractions.org>).

A number of pharmaceutical companies provide free drug level monitoring via the Liverpool University service:

- Roche:** patients receiving nelfinavir or saquinavir.
- Merck Sharp and Dohme:** patients receiving indinavir who are experiencing side-effects.
- GlaxoSmithKline:** patients receiving amprenavir.
- Abbott:** patients receiving lopinavir/ritonavir alongside amprenavir and/ or NNRTIs, and all children receiving lopinavir/ritonavir.



## Tenofovir in people new to HIV treatment

Following its recent approval in the European Union for use in people with prior experience of HIV treatment, new data have emerged on tenofovir in people new to HAART. Reports suggest that the nucleotide analogue is as effective as d4T at suppressing viral load and boosting CD4 count when taken in combination with 3TC and efavirenz. In addition, tenofovir appears to cause similar levels of moderate to serious side-effects as d4T, according to information available so far.

Preliminary 48 week study data from an ongoing three year double blind placebo controlled trial has been released by tenofovir manufacturer, Gilead. This safety and efficacy study is being conducted at 81 sites across the US and Europe, and has enrolled 600 people. Participants were randomised to receive either tenofovir, 3TC and the NNRTI efavirenz, or d4T, 3TC and efavirenz.

After 48 weeks of treatment, a similar proportion of people in the two study arms had achieved a fall in their viral load to below 50 copies: 82% for the tenofovir arm and 81% for the d4T arm. Similar increases in CD4 of around 168 cells were seen in each group. Overall, 9% of study participants withdrew because of side-effects.

Gilead will now apply to regulators in Europe for a license for the use of tenofovir in first-line therapy. *Source: Gilead press release.*

## Quality of life in efavirenz users

Spanish research suggests that people taking the NNRTI efavirenz have a higher quality of life than people taking protease inhibitors, despite the emotional disturbances reported by efavirenz users in the early weeks of therapy.

Researchers at Badalona University Hospital in Spain compared quality of life, measured using a standard patient questionnaire, in two treatment groups, both of which included people on their second anti-HIV treatment combination. One hundred participants were randomised to begin either an efavirenz-based regimen (51 people), or a protease inhibitor-based one (49 people).

After four weeks of treatment, 40% of the efavirenz group reported increased anxiety, irritability, sleep disturbances or light-headedness. In addition, almost 50% reported abnormal dreams, and two-thirds complained of dizzy spells. These are recognised side-effects of efavirenz therapy.

After 24 weeks, the number of people in the efavirenz group complaining of side-effects fell significantly, and by 48 weeks, 10% of efavirenz users noted abnormal dreams, 13% irritability, and 8% nervousness. At both four, and 48 weeks, the frequency of these side-effects were significantly lower in those receiving protease inhibitors.

Adherence levels, average fall in viral load, and

increase in CD4 count were comparable between the efavirenz and protease inhibitor groups. However, after 48 weeks, efavirenz-treated patients reported significantly greater improvements in their quality of life than those treated with a protease inhibitor.

The Spanish researchers stress that close follow-up of people receiving efavirenz-based regimens is recommended, particularly for those with a history of emotional disturbances. *Source: Fumaz. JAIDS 2002;29:244-253.*

## Encouraging results from T-20 trial

Adding the fusion inhibitor T-20 to a salvage regimen results in a significantly better viral load response after 24 weeks, and is well tolerated despite twice daily injections, according to preliminary results of a trial conducted in North America and Brazil.

Preliminary results of the phase III study of T-20 were released in April by manufacturer Roche. Individuals who received T-20 experienced a reduction in HIV viral load of approximately 97% compared with 76% for those in the control arm. Information is not yet available on the proportion of people with viral load below 50 copies at week 24, or on CD4 cell changes, though it is expected that more information will be presented at the World AIDS Conference in Barcelona in July.

Four hundred and ninety-one people with experience of all three classes of antiretrovirals, and viral load above 5,000 copies were randomised into two groups. Everyone received a four drug combination selected using the results of genotypic and phenotypic resistance tests. In addition, one group received T-20, whilst the other (the control arm) did not.

In the T-20 arm, 3% withdrew from the trial because of reactions at the area of the body where T-20 was injected. Insomnia, headache, dizziness and peripheral neuropathy were also more common in the T-20 arm.

A second T-20 study, TORO-2, is currently ongoing in Europe. The study has similar entry criteria and design. (Preliminary results were reported as this newsletter went to press and are available at [aidsmap.com](http://aidsmap.com)). Otherwise, T-20 is currently available only through an open label safety study in the UK, Europe and North America. Production problems mean that the manufacturer, Roche, only has enough drug to treat 450 new patients over and above those already recruited to clinical trials, and this situation will not change until late 2002. Roche are expected to apply for approval of T-20 late this year. *Source: Roche press release.*

## Tenofovir/ ddI interaction: warning on side-effects

Taking enteric coated ddI (*Videx EC*) and tenofovir with food leads to a 60% increase in blood levels of ddI, according to data released by tenofovir manufacturer Gilead in May. Whilst this raises the prospect of increased levels of ddI side-effects, how the interaction should be managed by doctors and patients is not yet clear.

In the US, ddI manufacturer Bristol-Myers Squibb has written to doctors alerting them to this new information. BMS said that it is evaluating the issue further, and in the meantime recommended the close monitoring of people taking both enteric coated ddI and tenofovir for ddI-related side effects, particularly pancreatitis, peripheral neuropathy and liver toxicities. More information is likely to be available by the time of the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) which takes place at the end of September, say BMS.

Medics and pharmacists in the UK offered a range of opinions on how co-administration of the two drugs could be managed when contacted by Keith Alcorn, editor of NAM's website [aidsmap.com](http://aidsmap.com). His detailed report can be read online at <http://www.aidsmap.com/news/newsdisplay2.asp?newsId=1466>.

### nam forum

June's NAM Information Forum takes place on Monday 24<sup>th</sup> June, from 7-9pm, at the University of London Union, Malet Street, London WC1. The subject is *Mental Health and HIV*.

The nearest tube station is Goodge Street. Refreshments, and a sign language interpreter, are available. These events are free and are aimed at people with HIV, and those who work in the field.





## credits

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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 includes: Anti-HIV Drugs, Clinical Trials, Glossary, Lipodystrophy, Nutrition, Resistance, and Viral Load & CD4.

**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.

**THT Living Well Phonenumber 0845 9470047 Mon-Thu 6-9pm**  
**i-Base Treatment Phonenumber 0808 8006013 Mon-Wed 12-4pm**

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



## subscriptions

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**AIDS Treatment Update is available on audio tape, and can be emailed to you as a pdf file for viewing with Acrobat Reader. Telephone NAM on 020 7627 3200 for details.**

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Inclusion in this newsletter of information on any drug or clinical trial in no way represents an endorsement of that drug or trial. This newsletter should always be used in conjunction with professional medical advice.

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