

aids treatment update

new HIV drugs coming in 2002

In this first issue of the new year we look forward to the expansion in HIV drug options which is expected as the year progresses. This new batch appears to include some interesting selling points – the promise of greater tolerability, and the ability to control HIV which is resistant to other treatments.

An alarming report from the USA – where HIV drugs have probably been more widely used than anywhere else – surfaced before Christmas, and provides convincing evidence that the demand for these new antiretrovirals will be considerable. Of a group of 2,000 HIV-positive Americans receiving medical care between 1996 and 1999, only a third had viral load controlled below detectable levels. Of those with detectable viral load, 78% had HIV which was resistant to at least one anti-HIV drug.

Of course many of the HIV drugs we in the UK might consider old-hat are not seen that way by the majority of people with HIV world-wide. Another optimistic forecast for 2002 is that wider global access to the full HIV medicine chest will continue to gather pace. UNAIDS estimate that five million people contracted HIV in 2001; most of these in sub-Saharan Africa, where one in ten adults have HIV, and as many as one in three in the worst affected regions.

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new drugs – tenofovir

2 first of a new class of anti-HIV drugs licensed, but how will it be used? by anna poppa

Tenofovir disoproxil fumarate is a new anti-HIV drug from the nucleotide analogue class of drugs. Tenofovir was recommended for licencing in the European Union, and in the US, in October 2001, and is expected to become available on prescription in the UK towards the end of January 2002. Tenofovir's indication within the EU is for the treatment of HIV in antiretroviral-experienced people only, though as we discuss later in the article, this limited approval is unlikely to prevent the drug being used in people who are taking HIV treatment for the first time. In the US, the drug was approved for use in both previously treated and untreated individuals.

How tenofovir works

Like the nucleoside analogues such as AZT and ddI, nucleotide analogues inhibit an HIV enzyme called reverse transcriptase. The physical difference between the two classes is that the nucleotides are active in their native form, unlike nucleosides that only work in cells that have the specific machinery to activate the drug by a process called phosphorylation. The important implication of this difference is that the nucleotide analogues may be active against HIV in a wider variety of infected cells.

Tenofovir and intensification

At present, information on tenofovir's clinical effects has been gathered in two key trials. Both of these involved participants who had taken antiretroviral therapy before, and who added tenofovir to their regimen, whilst their viral load was not fully suppressed, but in most cases was still at a fairly low level. This treatment strategy is sometimes called 'intensification'. Its success depends on several

factors, such as how high your viral load is when you intensify, and your previous treatment history, because this will determine your HIV phenotype – how susceptible your HIV is to the drug you'll be adding.

Intensification presents risks. Adding a single new drug to a regimen which is not suppressing viral load may lead that new drug to fail if it's not supported by other drugs which have some activity against HIV. For this reason, it's advised that if you change your treatment while your viral load is not suppressed, you should consider changing more than one drug, and ideally all of them. If treatment changes can be guided by the results of a resistance test (which provides information on your HIV genotype or phenotype), then some of this guesswork is removed.

Results from tenofovir studies

The two tenofovir trials which have reported results are:

- Study 902, which was a 'dose-ranging study'. (This type of study is performed in the early days of a drug's development, and compares several doses with the aim of establishing which should be taken forward into the next phase of development). Study 902 randomised participants to add either a placebo, or one of three doses of tenofovir, to their virologically failing anti-HIV regimen.
- Study 907, which randomised participants to add either a placebo, or the standard 300mg once daily dose of tenofovir to their virologically failing anti-HIV regimen.

Study 902 included 186 participants. On entry, all had detectable viral load, and the median value was just over 5,000 copies. The average CD4 count was 374 cells. Everyone had taken HIV treatment before, and was on treatment at study entry. The average time for which treatment had been taken was 4.6 years. For the first 24 weeks of the study, participants received either a placebo or tenofovir (75mg, 150mg or 300mg), all of which were taken once daily, and was allocated at random, and blinded. After 24 weeks, everyone on placebo was switched to tenofovir at the 300mg dose.

After 24 weeks, 19% of those receiving tenofovir had viral load below 400 copies, compared with 7% in the placebo group. The average fall in viral load was 0.6 to 0.7 log for those receiving tenofovir, and this was sustained to 48 weeks.

In study 907, 368 people added 300mg tenofovir to their anti-HIV regimen, and 184 added a placebo. Again, this allocation was randomised and blinded, and placebo recipients began tenofovir after 24 weeks. Participants had low level virological failure, i.e. between 400 and 10,000 copies. The median value was around 4,400. Median CD4 was over 400 cells, and median duration of prior treatment was 5.5 years.

The addition of tenofovir resulted in around a 0.6 log reduction in viral load which was maintained to 24 weeks. Proportions with viral load below 400 at 24 weeks were 42% in the tenofovir arm, and 13% for placebo. These differences are all significant.

Taking tenofovir

Tenofovir is dosed as one teardrop-shaped pale blue tablet once daily, preferably with food. A high fat meal probably helps absorption more than a low fat meal, and is certainly better than taking the drug on an empty stomach.

Tenofovir is cleared from the body through the kidneys and so avoids negative interactions with anti-HIV drugs (i.e. protease inhibitors and NNRTIs), and other medications which are eliminated via the liver. There is an interaction between tenofovir and the tablet formulation of

ddI though; ddI blood levels are substantially raised when taken with tenofovir. Researchers are currently evaluating whether the enteric-coated capsule formulation of ddI could be taken with food if combined with tenofovir, rather than without, as is currently required. At present, it is advised that tenofovir should be taken either two hours before, or one hour after taking ddI.

Tenofovir shouldn't be taken by people with kidney dysfunction, or alongside drugs which reduce kidney function, such as acyclovir, ganciclovir or cidofovir.

Side-effects

Considering the data which are available on tenofovir so far, the drug appears to have a relatively good record on side-effects. Of course, one of the most important lessons we've learnt about anti-HIV drugs in recent years is that a rosy short-term picture can turn much less fair during extended follow-up. Nevertheless, in studies so far, the frequency of higher graded, more severe side-effects – both those which were only seen in lab tests and those presenting with symptoms – was similar amongst those receiving a placebo and those on tenofovir, up to 24 weeks.

In the early days of its development, there were fears that tenofovir would cause serious kidney problems of the sort which had hampered adefovir, a forerunner to tenofovir, and which finally led to adefovir's demise as an anti-HIV drug. Kidney function is assessed by measuring levels of a waste product called creatinine, which is cleared through the kidneys. In the 902 study, raised creatinine was limited to Grade 1 severity only (the lowest grade), and occurred in 2% of people receiving the 300mg dose, so this appears not to be a significant problem with tenofovir.

Measured concern remains about tenofovir's effect on bone mineral density, after animal studies reported a condition called osteomalacia, where bone density is reduced. The changes were reversible, however, and it's worth remembering that these studies gave tenofovir at six to ten times the normal human dose. DEXA body scans conducted on (human)

UK access to tenofovir

Tenofovir will remain available on a named patient basis in the UK for individuals unable to construct a viable antiretroviral regimen without tenofovir, due to resistance and/or intolerance of currently licensed nucleoside analogues, until its final approval, expected at the end of January 2002.

different names for tenofovir

Tenofovir is made by Gilead Sciences and is known by several names. The full generic name of the drug is tenofovir disoproxil fumarate, which is shortened to tenofovir DF. Tenofovir DF is what's known as a prodrug. Once swallowed, the tenofovir DF tablet is converted in the body into tenofovir, and it's this simpler compound which is active against HIV. Tenofovir's company code-name is GS 4331, and its chemical abbreviation is bis(POC)PMPA, or simply, PMPA. Tenofovir is marketed in Europe and the United States as *Viread*TM. We'll be calling it tenofovir.

new drugs – tenofovir continued

participants in the 902 and 907 studies found no significant change in bone mass up to 48 weeks, but this (and effects on the kidneys) is something manufacturers, Gilead, are committed to monitoring, as this has been mandated by the US drug licencing agency, the FDA.

Metabolic abnormalities such as those seen in the lipodystrophy syndrome have not been associated with tenofovir treatment so far. In the 907 study, there was no difference in the frequency of moderate to severe raised lipids or triglycerides, up to 24 weeks, between tenofovir and placebo recipients. Though raised triglycerides do feature with longer follow-up, this cannot be linked to tenofovir specifically, but to individuals' anti-HIV treatment generally.

Tenofovir is less likely to be associated with mitochondrial toxicity than nucleoside analogues such as ddC, ddI and d4T. For example, the uptake of tenofovir into polymerase gamma (the part of mitochondria negatively affected by nucleoside analogues) is a hundred-fold lower than the uptake of d4T.

In extended follow-up of participants from the 902 study, the only adverse events of greater than Grade 3 severity which occurred during a median of 100 weeks follow-up, were depression and asthenia (weakness). However, these occurred in four and one of a group of 54 people respectively, who were assigned the 300mg dose in the original randomisation. These individuals were taking other medications alongside tenofovir and so it's not possible to say whether these effects were caused by tenofovir.

Tenofovir and drug resistance

Somewhat unusually, Gilead have concentrated the initial phases of tenofovir's development on its efficacy in people who have used HIV treatments before, have at least a degree of

drug resistance as a result, and so now need therapies which will be active against resistant viruses. So there's been an emphasis on gathering resistance data, and understanding which viral geno/phenotypes present the greatest likelihood of responding to tenofovir.

To explain this further; each time an HIV drug regimen fails to reach the target of suppressing viral load to very low levels, there's a risk that HIV strains will emerge which are resistant to drugs in that regimen. These resistant strains are called *mutants*, and once they appear in the circulation of someone taking drugs, they never really go away. This is important because they are often resistant not just to one HIV drug, but to other similar ones too. This is called *cross-resistance*.

There's a degree of cross-resistance between tenofovir and drugs in the nucleoside analogue class. This means that your past experience of taking nucleosides may affect your response to tenofovir, *if* you acquired resistance to the nucleosides you took. The degree of response appears to vary according to the specific mutants you may carry – that is, your viral genotype or phenotype. This is quite complicated, but to summarise what we know about response to tenofovir in treatment-experienced people based on available data:

- Response to tenofovir is strongly influenced by the presence of TAMs – thymidine analogue mutations. AZT and d4T are thymidine analogues, and TAMs is the name given to mutations which confer resistance to one or both of these two drugs. If you've never taken AZT and d4T, you will not have any TAMs, (so long as you didn't acquire these resistant viruses when you were infected). If you have taken either of these drugs, you *may* have TAMs.
- People with one or more TAMs can expect to respond to tenofovir, but they may do less well than people who have no TAMs.
- If you have three or more TAMs, and one of them is either M41L or L210W, you can expect to do less well on tenofovir. If you have three or more TAMs but *none* of them

are M41L or L210W, then you *can* expect to respond to tenofovir.

- People with the 3TC resistance mutation, M184V, can expect to respond to tenofovir, but again, the response is best in people who have no TAMs alongside this mutation. M184V can also occur in response to abacavir.
- The K65R mutation is associated with resistance to tenofovir, and so if you have this mutation, you wouldn't be expected to respond to the drug. K65R is also associated with treatment with ddI, ddC and (rarely) with 3TC. However, it's an uncommon mutation.

All of this information highlights the importance of drug resistance tests to guide changes in treatment, and the need for expert interpretation of the results.

Where will tenofovir be used?

Given this evidence of tenofovir's effectiveness in people with drug resistance, its approval raises the familiar question – where will it best be used? Tenofovir's European licence restricts its use to people with experience of HIV treatment, because there are currently no significant data on the drug from trials involving people who are new to treatment. In practice, however, once a drug is available on

prescription, doctors can and will prescribe it for other uses, so long as they deem this to be necessary and appropriate, and they take personal responsibility for this 'off-label' usage.

Antiretrovirals typically perform best in people who are new to treatment, and so tenofovir should be expected to be at least as active as a first-line drug as it has been in people with drug experience. Because it's relatively simple to take, and appears to cause fewer side-effects – at least over the short-term – than several other drugs, it may be an attractive choice to people who are starting treatment for the first time. It's also active against hepatitis B virus, so people who are co-infected may have a further reason to consider the drug, though there are few data on its use in this setting currently.

Gilead's 903 study is investigating the effects of tenofovir as part of first-line therapy, and we understand that results may be reported from this study by the late Spring. However, the 903 protocol compares efavirenz/3TC/tenofovir with efavirenz/3TC/d4T, and Gilead currently have no further plans to evaluate their drug in naïve patients. This points to a likely shortage of data from randomised trials on other tenofovir-containing regimens. For example, people considering taking tenofovir with two nucleoside analogues, will have little information to inform their decision, and this situation may not improve quickly.

key conclusions

- Tenofovir is a new type of anti-HIV drug which is about to become available in the UK and Europe for people who've taken HIV drugs before. In future, it may well also be licensed for use in people who are new to treatment.
- Tenofovir's effectiveness has been demonstrated in people who added it to their HIV drug regimen when they had early viral load failure. This may not be the best way to use the drug – it may be better to begin it alongside other drugs likely to be active against your HIV.
- Tenofovir is dosed as one pill taken once a day, with food, and appears to be relatively well-tolerated, based on the information we have about its side-effects so far.
- If you've taken HIV drugs before, your response to tenofovir will be affected by the nucleoside analogues you've used, and whether you developed resistance to them.
- There is no information from trials so far on the use of tenofovir by people who are new to treatment, but this information will be available in the near future.

glossary

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antiretroviral Substance which 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.

cholesterol A waxy substance, mostly made by the body and used to produce steroid hormones.

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

genotype The genetic make-up of an organism.

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

lipodystrophy A disruption to the way the body produces, uses and distributes fat.

metabolism The mechanisms which sustain life, turning sugar and fat into energy.

naïve Never having taken anti-HIV treatments before.

NNRTI Non nucleoside reverse transcriptase inhibitors, family of antiretrovirals that includes efavirenz and nevirapine.

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new drugs – atazanavir

6 early data on this new once daily drug continue to suggest it does not raise blood fats like others in its class by [anna poppa](#)

Atazanavir is an experimental protease inhibitor (PI) being developed by Bristol-Myers Squibb. It was previously known as BMS-232632. Atazanavir is currently entering Phase III of its development, which means that more substantial numbers of people will gain access to the drug, though only through participation in clinical trials.

Atazanavir versus other PIs

So far, most of what we know about this drug emanates from trials investigating its use in people who had not taken HIV treatments previously when they began atazanavir. The most significant of these studies so far is codenamed AI424-008, and 48 week results were presented last October at a European HIV conference in Athens.

The study compared two doses of an atazanavir-based HAART regimen (400mg or 600mg, once daily), to one containing nelfinavir, another PI. All participants also received d4T and 3TC, and were allocated the PI component of their regimen at random. Four hundred and sixty-seven people were recruited, all of whom had viral load above 2,000 copies and CD4 counts over 100 cells. The median values at entry were around 55,000 copies and 270 cells respectively.

Overall, the study found that viral load responses between the arms were comparable. At week 48, 65% in both atazanavir arms had viral load below 400 copies, compared with 58% of the nelfinavir group. The proportions with viral load below 50 copies were substantially smaller, at 31% in the atazanavir 400mg group, compared with 36% in the 600mg group and 38% in the nelfinavir group. CD4 cell increases were comparable at week 48, at around 210-240 cells above baseline.

Preliminary results from study BMS-009 were presented at a conference in Chicago before Christmas. Eighty-four people on a virologically failing PI regimen were randomised to receive either atazanavir/saquinavir (at one of two doses), or ritonavir/saquinavir, plus two nucleoside analogues. Viral load response appeared similar across arms at 24 weeks.

Taking atazanavir

Atazanavir is the first once daily PI, and has a low pill burden of two pills when taken as a sole PI (two 200mg capsules). If combined with another PI, the dose may be different to the standard 400mg dose, and this is under investigation within clinical trials. Drug levels are raised when atazanavir is taken with food.

Preliminary drug interaction testing shows that atazanavir levels are reduced when administered with the tablet version of ddI.

Side-effects

Though it's very early days in the development of atazanavir, the drug has attracted interest because it *appears* that it may not cause the increases in blood lipids which affect the other drugs in this class. Because raised blood lipids present a risk of cardiovascular disease (see last month's *ATU*), and because these changes in the blood appear connected to the body fat changes termed lipodystrophy, this side-effect has caused significant concern.

In the AI424-008 study noted above, atazanavir was not associated with any significant increase in cholesterol or triglyceride levels over the 48 week period, whereas significant increases did occur in the nelfinavir arm. At week 48, the average percentage increase in total cholesterol for the atazanavir 400mg arm was 5%, a non-significant change from baseline, compared to 25% in the nelfinavir arm. Similar differences were seen when LDL ('bad') cholesterol and triglycerides were analysed (5% versus 23%, and 7% versus 50% respectively).

In the BMS-009 study, total cholesterol increased amongst recipients of ritonavir/saquinavir at week 24, but was either unchanged or reduced in those receiving atazanavir/saquinavir.

High bilirubin levels have been reported quite frequently with atazanavir. Bilirubin is a pigment found in bile, which is produced by the

liver as an aid to digestion. Whilst the increase in bilirubin may not in itself be harmful, it can result in jaundice, a yellowing of the skin. In the AI424-008 study, nineteen people who were taking a 600mg dose of atazanavir reduced their dose because of Grade 4 (severe) increases in bilirubin. There were four cases of jaundice in this arm of the study. Overall, the incidence of Grade 3 or 4 hyperbilirubinemia was high in both atazanavir groups; a frequency of 32% in the 400mg group, and 52% in the 600mg group.

Other than this, the main side-effect of atazanavir was diarrhoea, which was reported in approximately 30% of atazanavir recipients in AI424-008, compared with 60% of those taking nelfinavir.

Atazanavir and resistance

Though atazanavir is now being studied in people who have used other PIs before, our understanding of its resistance profile is currently based only on information from test-tube studies. In a study of 63 HIV isolates taken from PI-experienced individuals, a third with reduced sensitivity to three PIs, and two thirds with reduced sensitivity to four or more PIs, were also less susceptible to atazanavir. It's not clear yet whether boosting levels of atazanavir through the addition of another PI might offer the means to overcome drug resistance in some individuals.

The primary mutation which is associated with resistance to atazanavir appears at codon N88S. However, HIV with this single mutation remains sensitive to other PIs according to test-tube studies.

key conclusions

- Atazanavir is an experimental protease inhibitor now entering a new phase of development which will test the drug in people who've already taken HIV drugs.
- Trials suggest atazanavir's effectiveness is comparable to other protease inhibitors in people new to treatment.
- Atazanavir is taken once daily and the pill burden is low.
- So far, atazanavir appears not to disrupt levels of fats in the blood in the way that other protease inhibitors commonly do. It does, however, cause jaundice in some people.

atazanavir studies recruiting in the UK

As we mentioned in last month's *News in brief*, a series of trials evaluating atazanavir are now recruiting participants at centres across the UK. These are designed to investigate the potential uses of atazanavir in people with drug experience. Details of these trials, including participating UK centres are available on NAM's website, aidsmap.com.

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new drugs – T-20

8 production problems continue to delay access to first HIV fusion inhibitor, but T-20 could be in pharmacies by year end by *anna poppa*

T-20 is the first of a new class of drugs called fusion inhibitors, so-called because they stop HIV from binding to and entering human cells.

T-20 is being developed by Trimeris Pharmaceuticals, and is also known as pentafuside. Trimeris have agreed a marketing and development relationship with Roche Products to commercialise the compound.

T-20 is currently being tested in trials evaluating its safety and efficacy in people who have taken anti-HIV drugs before. The drug has not been used in people with HIV who are taking antiretroviral treatment for the first time, and is unlikely to be used in this way in the near future.

Taking T-20

T-20 is not available in pill form. Instead, it is administered by injection under the skin (subcutaneously). This is performed at home by the

patient after training from their health care team. T-20 is a drug for people who have no other viable treatment options, and so most people find the process of injecting it manageable, though it's quite complicated, involving several steps to reconstitute the freeze-dried drug using sterile water.

Effectiveness of T-20 in trials

Lalezari randomised 71 protease inhibitor (PI)-experienced, NNRTI-naive people to 50, 75 or 100mg T-20 twice daily, plus amprenavir/ritonavir, efavirenz and abacavir. A control group received these latter four drugs only. At baseline, median viral load was around 19,000 copies and CD4 count was 232.

At week 16, viral load had fallen by -2.84 log in the 100mg T-20 group, compared to -2.16 log in the control arm. For those with baseline viral loads above 20,000, median change in viral load at week 16 in the pooled T-20 arms

was -2.64 log compared to -1.55 log in the control arm.

A separate study, T20-205, evaluated a 50mg dose of T-20 given twice daily to seventy people. At study entry, the median viral load was 5 log (100,000 copies) and the median CD4 count was 90 cells. All participants received T-20 plus a background regimen selected according to the results of a genotypic drug resistance test. On average, participants took five additional antiretrovirals with T-20. 79% of participants were experienced with all three currently used HIV drug classes, and the median number of prior antiretrovirals was nine.

Over the 48 weeks of study, thirty people discontinued treatment: fourteen for virological failure, seven withdrew voluntarily, four were lost to follow-up, three for adverse events (none of which were related to T-20), and two for non-adherence. On-treatment analysis at 48 weeks found that 22% had viral load below 50 copies, 39% were below 400 copies, and 61% had maintained a viral load that was at least one log below their baseline level. In an intent-to-treat analysis, 13% had viral loads below 50 copies, 23% below 400 copies, and 33% maintained at a least a one log drop in viral load from baseline.

Side-effects

The only significant side-effect reported so far is the development of adverse reactions around the injection site. These have been reported in two-thirds of those who have taken T-20 and may take the form of an itchy rash, red, swollen or puffy skin, hardened skin, or cysts or nodules forming at the injection site. More rarely, a number of individuals have developed abscesses at the injection site. These rashes and

reactions may occasionally require treatment with antihistamines or painkillers.

Resistance

Just like other antiretrovirals, resistance to T-20 can emerge rapidly if it is not supported by other drugs which are active against HIV. T-20 is active against a wide variety of resistant HIV isolates in test tube studies. A second fusion inhibitor, T-1249, is also in development, and there does not appear to be complete cross-resistance between the two drugs, meaning that resistance to T-20 *may* not preclude the use of T-1249.

Future development and access

Ongoing trials are evaluating T-20 within salvage regimens, and an international open-label safety study, T-20-305, is expected to open before April. This will provide the drug to treatment-experienced people with CD4 cell counts below 50 and viral load above 10,000 copies, with preference given to those with a recent AIDS-defining illness or cancer. There are 15 places on this study allocated to the UK, and 450 worldwide.

Roche are expected to file for T-20's approval in the European Union and the US in April 2002, and if approval is granted, the drug could be available on prescription by the end of the year. However, T-20 is an unusually large molecule, and Roche have encountered substantial problems scaling up supply of peptide, T-20's key component. Whilst continued discussion of the manufacturing challenge appears to be exacerbating impatience amongst some treatment activists, it may also be priming the market for a likely high price tag. These factors could together limit T-20's use, even when licenced.

key conclusions

- T-20 is a new type of anti-HIV drug from a class called fusion inhibitors.
- T-20 is self-administered by injection.
- T-20 is not licensed at present, but may become more widely available over the course of 2002. It will be used first in people who have very limited HIV treatment options, and will not be available to people taking treatment for the first time.
- T-20 appears effective against HIV and appears to cause few side-effects, according to research studies so far.

glossary

Continued from page 5 nucleoside analogues

Family of antiretrovirals which includes AZT, ddI, 3TC, d4T, abacavir and ddC.

phenotype Trait or behaviour which results from a particular genotype.

placebo A pill which looks and tastes exactly like a real drug, but contains no active substance.

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

randomisation The process of selecting by chance the treatment that a clinical trial participant will receive.

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

resistance A drug-resistant HIV strain is one which is less susceptible to the effects of one or more anti-HIV drugs because of its genotype.

triglycerides The basic 'building blocks' from which fats are formed.

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.

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Lalezari J et al. 13th International Conference on AIDS, abstract LBP116, 2000.

Garlic supplements and saquinavir – not a good mix

A common dietary supplement may prevent certain anti-HIV drugs working properly, according to a recently published US study. Researchers observed that garlic supplements sharply reduced blood levels of the protease inhibitor saquinavir.

Garlic induces, or speeds up, the activity of the CYP 450 enzyme system which is responsible for metabolising saquinavir. It's possible that this effect pushes saquinavir through the body faster than usual, lowering the concentration in the blood. Other protease inhibitors, and the NNRTIs efavirenz and nevirapine, also pass through this system, but it's not clear from this new research if garlic supplements will affect these drugs in the same way.

The research team advise that garlic supplements should not be used by people who are taking saquinavir (either as *Fortovase* or *Invirase*) as their sole protease inhibitor. Again, it's not clear whether this advice should apply to all PI or NNRTI users, or to people who take saquinavir with another PI.

Reference: Piscitelli SC et al. *Clinical Infectious Diseases* 34 (Electronic Edition), 2002.

Living with HIV – impact on mental health assessed

Despite the availability of effective antiretroviral treatments, living with HIV may still be associated with significant mental health problems, according to a report from the Swiss HIV Cohort Study recently published in the *Journal of AIDS*.

Levels of anxiety and depression, and quality of life, were assessed in 397 people with HIV using a series of self-completed questionnaires. Anxiety and depression were common, and there was a clear relationship between social factors such as having a job and the mental health parameters measured – being employed was linked to better scores. Whilst high viral load tended to predict poor mental health scores, this was not true of low CD4 counts. However, the duration people had been living with HIV *was* associated with anxiety and depression, independent of other factors. Scores tended to be worse for intravenous drug users than people exposed to HIV via other transmission routes.

The authors argue that these findings have implications for the long-term care of HIV-positive people; both to enable individuals to cope with their diagnosis, and because

improved mental health is likely to facilitate better adherence to HIV treatments.

Reference: Zinkernagel C et al. *JAIDS* 2001;28:240-249.

Cholesterol lowered by frequent eating

A large population-based study performed in Norfolk has found that people who eat frequently throughout the day have lower cholesterol levels than people who eat just once or twice.

The study observed 14,666 men and women aged 45-75. Average levels of both total cholesterol and LDL cholesterol (the 'bad' sort), decreased as the daily frequency of eating increased. Average cholesterol concentrations were 0.25 mmol/L lower in those who ate more than six times a day compared to those who ate once or twice. This difference fell to 0.15 mmol/L when factors which may have influenced the results (such as smoking, age, obesity, physical activity, and alcohol and nutrient intake) were controlled for.

As this is a UK general population study, the vast majority of participants should be expected to be HIV-negative. These effects may be different in people with HIV.

Reference: Titan SMO et al. *British Medical Journal* 2001;323:1-5.

US urges all HIV+ve people to test for HCV

The US Federal government authorities have recently released guidelines on the prevention of opportunistic infections in people with HIV. Guidance was last revised in 1999. Among the key changes in 2001, is the recommendation that everyone with HIV should be screened for hepatitis C virus infection.

Reference: 2001 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in

Persons Infected with Human Immunodeficiency Virus at <http://www.hivatis.org/trtgdIns.html#Opportunistic>

Undiagnosed HIV common in the UK & worst amongst Africans

Estimates from anonymous HIV testing programmes suggest that one third of people living with HIV in the UK remain unaware of their status. Among heterosexuals the proportion remaining undiagnosed is closer to 50%. This latter group consists overwhelmingly of black Africans. According to a new report, HIV-positive black Africans are more likely to be diagnosed late in the course of disease than their white counterparts, reducing their ability to benefit from HIV treatments.

In a recent letter to the journal *AIDS*, researchers from two London HIV clinics, the Mortimer Market Centre and Newham General Hospital, reviewed all adults diagnosed with HIV infection between January 1998 and December 1999 at one of these clinics, and drew comparisons with those diagnosed at the same centres between 1982 and 1995.

In the period 1998-1999, the median CD4 cell count at diagnosis was 188 cells for black Africans and 380 cells for non-Africans. This compares with 277 cells for black Africans, and 440 cells for non-Africans diagnosed with HIV between 1982 and 1998.

The risk of developing opportunistic infections increases as the CD4 count falls below 200 in untreated people, and the effectiveness of anti-HIV therapy is reduced, making the decline in CD4 count at time of HIV diagnosis among black Africans particularly worrisome. Thirty-five per cent of black African patients diagnosed between 1998-99 had an AIDS-defining illness within one month of their HIV diagnosis, compared to 13% of non-Africans.

Reference: Burns F et al. *AIDS* 2001 7;15(18):2453-2455.

NAM forums 2002
NAM's popular Patient Information Forums continue in 2002 at the usual venue in central London: University of London Union, Malet Street, WC1. These events are free and open to all who want to attend. Each month a special guest speaker discusses an HIV treatment-related topic, and answers questions from the audience. A sign language interpreter is available and refreshments are provided. Forums runs from 7-9pm and dates for the coming months are: January 28, February 18, March 25, April 29. January's forum is on new HIV drugs, as reviewed in this issue of *ATU*, so if you have been left with questions, please come along.





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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.

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.



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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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