

# aids treatment update

## special issue – which HIV drugs first?

During this year's Autumn programme of HIV conferences, the key turf-war has been over which drugs to use when starting anti-HIV therapy for the first time. This is an issue which predominates every once in a while, often spurred by the anticipated arrival of new products to the HIV therapy marketplace.

This occasion is much the same – significant new treatment options have become available in the US, and are either here or expected soon in the UK and rest of Europe. Doctors and patients must consider where these new products fit with existing options, and with evolving treatment issues. When the term 'protease-sparing' was first coined two years ago to mean a three drug regimen other than the then-standard protease inhibitor (PI)-based HAART, it fitted with an emerging consensus that treatment needed to be easier to take if long-term adherence were to be expected of the majority. Now, newer regimens, some involving old drugs, have challenged the view that some drug classes are 'easy' and others 'hard'. Similarly, worries about long-term side-effects can be attributed fairly evenly across classes.

In this special issue, we round off the year with a guide to choosing treatment and a class by class review of the latest information on first-line antiretroviral options.

choosing treatment 2

starting with PIs 4

starting with NNRTIs 6

starting with NRTIs 8

news in brief 11

# choosing treatment

## 2 how to choose an initial HIV drug combination from the available options by anna poppa

While the issues have changed since *AIDS Treatment Update* last reviewed this subject a year ago, and there have been interesting new data, there remains no clear answer to the question of which anti-HIV drugs to use first. HAART regimens continue to be assembled according to the summary box opposite, and according to the relative significance to the individual of the principles outlined below. These principles are in no way mutually exclusive, however, and each has an important place in the decision-making process.

### Principle one: sequencing

At a recent international HIV conference held in Glasgow, doctors from three English HIV clinics, one in London and two outside, presented information about which treatments people with HIV start on and why they change<sup>1</sup>. The analysis included 759 people beginning first-line therapy during 1998 and 1999. Many found their first combination was effective for a limited period of time, and that each subsequent combination was replaced sooner than the one before.

In this scenario, where all drug classes have their turn at some stage, it's vital that – as far as possible – each person gains the most benefit they can from each available drug class. If we assume that all anti-HIV drug combinations will fail at some point, then an appropriate strategy would be to plan for that failure by selecting regimens with a view to ensuring that future options will not be closed off. This strategy is called drug sequencing.

The traditional view of sequencing has focused on drug resistance as the major spoiler of future options, (see sidebar on page 3 – cross resistance). Now, there's perhaps more discussion of the role of other causes of treatment failure, such as needing to change drugs in order to manage side-effects.

### Principle two: potency & durability

A more optimistic view suggests that not all drug combinations are doomed to failure – or at least not at the same speeds – so long as they involve that winning combination of being manageable for the patient, and being sufficiently potent to achieve, and maintain, the upper hand against HIV. Browsing the ads which pharmaceutical companies use to promote HIV drugs to doctors and patients shows that this is the party line – 'tough on HIV, easy on the patient'.

The aim of anti-HIV therapy is to prevent further immune damage and subsequent illness by reducing viral load to minimal levels. While this is an important goal for everyone, whether all three-drug regimens are sufficiently potent for people who begin with higher viral load levels, e.g. above 100,000 copies, has been debated – most particularly in relation to abacavir-based regimens and nevirapine-based regimens. The review of English HIV patients highlights that this remains an important clinical question: in those who began three-drug HAART, median viral load at the time of starting was 110,000 copies, and median CD4 count was 190 cells.

#### which NRTI backbone?

Initial HIV drug regimens include (at least) two NRTIs. How to choose this NRTI backbone will be covered next month.



**PI [protease inhibitor] see pages 4-5**

**NNRTI [non nucleoside reverse transcriptase inhibitor] see pages 6-7**

**NRTI [nucleoside reverse transcriptase inhibitor or nucleoside analogue] see pages 8-9**

### Principle three: easy-to-use

Enabling long-term use of a regimen requires long-term 'manageability' for the person taking it to be prioritised. Whilst long-term adherence is about other things as well as this, taking treatment which impinges on quality of life will always be an uphill struggle. The number of pills to be taken, the number of doses per day, and the food, drink and fasting requirements of a regimen will be important to fit with the individual's daily activities and with their preferences.

### Principle four: safety & tolerability

All drugs are associated with unwanted effects, but they may be more or less

significant to different individuals. For some, central nervous system side-effects may be a less worrying prospect than diarrhoea, and *vice versa*. Avoiding side-effects which impact negatively on quality of life is an important end in itself. The tendency for drug-related symptoms to interfere with adherence is another reason to prioritise tolerability.

The issue of tolerability is the counter-balance to the desire for potency. So while regimens of four, five and six drugs may offer greater potency, the reason these are not standard options for first-time therapy is because they would likely result in an unacceptable level of side-effects.

### which first-line anti-HIV combination is best?

- There is no clear evidence as to which of the currently available drug combinations is best for people starting HIV treatment, so doctors advise choosing drugs according to the individual needs of the patient.
- It's usual to begin with three drugs, two of them being nucleoside analogues (NRTIs).
- A combination of one NNRTI and two NRTIs appears at least as effective in reducing viral load below 50 copies as a combination of a protease inhibitor (PI) and two NRTIs.
- A combination of three NRTIs is another option, but in the past this has appeared less satisfactory therapy for people who begin treatment with high viral load.
- There is a relative lack of evidence about the effects of regimens with an NNRTI or a third NRTI in people with advanced disease, compared to PIs.
- The longer-term safety of anti-HIV therapy is an ongoing concern that affects all drug classes to an extent.

### cross resistance

Viruses resistant to one anti-HIV drug are often resistant to other similar drugs as well. Changing to an effective new drug combination in these circumstances may be difficult. This problem affects all classes of anti-HIV drugs. E.g. developing resistance to one NNRTI is likely to stop you benefiting from other available drugs in that class. This is a key reason why regimens containing drugs from each class (PI, NNRTI, NRTI) are rarely used first-line. If resistance to all classes develops, finding an effective second regimen will be hard.

### sequencing studies

Two large international studies are investigating the longer-term outcomes of differently sequenced anti-HIV drug regimens. INITIO is recruiting participants in the UK. A US study, ACTG 384 closed to recruitment a year ago, and may report initial results in 2001.

### further reading

The subject of this special issue has been previously covered in issues 83, 76 and 68, and more detailed reviews of the issues raised, drugs discussed, and current UK clinical trials can be found on NAM's website [aidsmap.com](http://aidsmap.com).

# starting with PIs

4

The protease inhibitor (PI) class of drugs was the first associated with the big swings towards better and longer life and health seen in people with HIV in industrialised countries in the late 1990s. As alternatives became available which seemed no less potent, but promised simpler dosing, PIs became less popular. Now they're experiencing something of a comeback.

Taking one PI with a low dose of ritonavir tends to boost levels of the other drug, and this has been a good thing for several different reasons. In the case of hard-gel saquinavir, it has allowed a drug which was only weakly potent as a sole PI because of poor absorption, to be used effectively. With indinavir, the addition of ritonavir allows twice daily dosing of both drugs and a removal of dietary restrictions. And with a new PI, ABT-378 (lopinavir), there's some evidence that the high blood levels obtained through the ritonavir boost can overcome resistance to PIs, and therefore allow people to benefit from a second PI-containing regimen.

## ABT-378/r in first-line therapy

ABT-378/r (lopinavir/ritonavir) has now been approved for use in the US, under the brand-name *Kaletra*, and will soon come up for consideration by European Union drug-

licensing authorities. It is produced by Abbott Laboratories, who also make ritonavir.

There have been two major studies investigating its use in first-line therapy. Study M97-720 randomised 100 treatment naïve people, with viral load above 5,000 copies, to receive one of three ABT-378/r doses, taken twice daily together with d4T and 3TC<sup>2</sup>. After 48 weeks, everyone who was not already taking ABT-378/r at the 400mg/100mg twice daily dose was switched to that dose.

At entry, median viral load was 63,000 copies and median CD4 count was 326 cells. After 96 weeks of treatment, 78% had viral load below 50 copies using an intent to treat analysis, (see sidebar page 9 – analysing data). According to the on treatment analysis the proportion below 50 copies was 92%.

Fifteen people left the study at or before 108 weeks, in three cases for study drug-related side-effects. The most common side-effects were diarrhoea (25%) and nausea (15%). Raised cholesterol and triglycerides were seen in 15% and 13% respectively, but as values at entry were not reported, it's unclear if these were associated with treatment.

Study M98-863 compared ABT-378/r/d4T/3TC with nelfinavir/d4T/3TC in 653 people who were new to treatment and had viral load above 400 copies<sup>3</sup>. Treatment was blinded and was allocated at random. Nelfinavir was given three times daily, though a switch to twice daily was allowed at 24 weeks.

At entry, median viral load was 79,000 copies and median CD4 count was 259 cells. By intent to treat analysis, the proportion with viral load below 50 copies at 48 weeks was 67% for ABT-378/r and 52% for nelfinavir. By on treatment analysis, proportions are 83% and 68% respectively. These differences are significant and reflect results from 262 ABT-378/r users and 251 nelfinavir users who had reached the 48 week point.

There was no difference in side-effects and laboratory abnormalities between groups, except for a higher incidence of raised

triglycerides amongst the ABT-378/r arm (9% versus 1%). More people left the nelfinavir arm than the ABT-378/r arm, however; 24% versus 17% overall, including 4% versus 2% for study drug related side-effects, and 9% versus 1% for virological failure (nelfinavir versus ABT-378/r respectively).

### Where is ABT best placed?

Abbott Labs designed ABT-378/r with the intention of developing a PI which would be useful to people with PI resistance. Results from two studies investigating ABT-378/r use after other PIs have supported Abbott's theory that if drug levels are high enough, they can overcome drug resistance (see *AIDS Treatment Update* issue 92). Both involved the use of ABT-378/r plus an NNRTI in people who were PI-experienced but NNRTI naïve, but nevertheless, in people with experience of several different PIs, response rates increased as baseline sensitivity to ABT-378/r grew<sup>4</sup>.

So far, there is relatively little information on how resistance to ABT-378/r develops. Participants from the nelfinavir comparison study, who had viral load above 400 copies at week 24 and week 48, were given a genotypic resistance test to look for protease drug resistance mutations. Results were available for 64 of 78 nelfinavir users and 31 of 42 ABT-378/r users. Mutations were found in 20 nelfinavir users but were not detected in any ABT-378/r user. Similarly, of four people who had viral rebound in the M97-720 study, none had genotypic resistance to ABT-378/r, though two were resistant to 3TC<sup>5</sup>.

A report from the VIRADAPT study, (which looked at the role of resistance testing in the selection of salvage regimens for people whose treatment was no longer suppressing their viral load), found evidence that ritonavir resistance mutations emerged during treatment with 100mg ritonavir (given twice daily with 600mg saquinavir)<sup>6</sup>. The VIRADAPT team suggest therefore that the use of this 'baby-dose' of ritonavir in people new to treatment – for example those taking ABT-378/r – might also result in the development of ritonavir resistance mutations. This theory too, requires further testing; the

development of resistance mutations in people who've previously taken several different drugs could be different to that seen in people new to treatment.

Despite the absence of ABT-378/r mutations in people with viral load rebound on ABT-378/r in clinical trials so far, it would be foolhardy to assume that this will be repeated in 'real-world' settings, where failure rates are higher, where monitoring may be less intensive, and where many people do not come off treatment at the first hint of a viral load rebound. These are the ingredients for drug resistance.

For some doctors, ABT-378/r's proven effectiveness in PI salvage, and the relative lack of information both on how people who fail on ABT-378/r will themselves be salvaged, and on the drug's effect on blood lipids, means ABT-378/r may be best saved for use after other PIs have failed.

According to Professor Brian Gazzard, of the Chelsea and Westminster Hospital, "It's the outcome of the second treatment – i.e. salvage – that largely determines what will happen in ten years time rather than the potency of the initial regimen. Thus all studies and all drugs need to be looked at for durability and for 'salvage-ability' as much as for initial potency. There's uncertainty over ABT-378 mainly because we don't know why it fails and therefore what salvage is going to be possible. It's certainly durable and potent."

### Other boosted PIs

A further criticism levelled at ABT-378/r is that its potency is the result of ritonavir-boosting, and as such, it may be no more effective than other boosted PIs. At present there are no data from comparative trials, though a US study called MaxCmin II comparing ritonavir/saquinavir with ABT-378/r will begin shortly, a Roche-funded Danish

### glossary

#### adherence

The act of taking a treatment exactly as prescribed.

#### antiretroviral

A substance that acts against retroviruses, e.g. HIV.

#### baseline

Starting point or value.

#### CD4

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

#### HAART

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

#### hepatitis

Inflammation or infection of the liver.

#### lipid

A general term for fats.

#### naïve

Never having taken anti-HIV drugs before.

#### open-label

A clinical trial where both the researcher and participants know who is taking the experimental treatment.

#### regimen

A drug 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.

#### salvage therapy

Any drug regimen used after a number of earlier regimens have failed.

#### 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 with PIs continues  
on page 10

# starting with NNRTIs

6

Efavirenz and nevirapine, the two licensed drugs in this category have become popular first-line options. In 1998 and 1999, half of those who began anti-HIV therapy in three English HIV clinics took an NNRTI-based three drug regimen, whilst a quarter began a PI-based triple regimen (see diagram page 8)<sup>1</sup>.

In addition, the trend for switching off an existing suppressive regimen to improve tolerability has favoured these drugs. Both are simpler regimens than many PIs, and for those concerned about metabolic abnormalities and lipodystrophy, there is some evidence that switching to nevirapine may improve dysregulated blood lipids. The evidence that efavirenz can help here too is less strong, and neither have been convincingly shown to improve body shape changes. (This subject was last covered in *AIDS Treatment Update* issue 87, and will be the subject of a forthcoming

special issue. See also the comprehensive reviews on our website, [aidsmap.com](http://aidsmap.com).)

Earlier studies have suggested that efavirenz may be a more potent first-line therapy than indinavir. Nevirapine was found comparable to indinavir therapy in the Atlantic study, and has also been compared with nelfinavir in the COMBINE study.

## Nevirapine versus nelfinavir

In COMBINE, 142 people who were new to anti-HIV therapy were randomised to receive open-label treatment with *Combivir* plus either nevirapine or nelfinavir<sup>12</sup>. All drugs were taken twice daily. Median viral load was approximately 60,000 and median CD4 cell count was approximately 355 at entry.

After 36 weeks treatment, viral load responses were better in the nevirapine arm: 67% versus 38% below 20 copies by intent to treat analysis, and 80% versus 56% in the on treatment analysis. These differences are wider than may have been expected given previous nelfinavir data, and they are not easily explained. More people stopped their nelfinavir treatment than stopped nevirapine (32 versus 24 at 36 weeks), though some of these switched because of intolerance, roughly equal numbers in each. A higher number of nelfinavir users were lost to follow-up (17 versus 10). Fewer nelfinavir users were reported to be more than 95% adherent to their treatment in the first month (59% versus 79%). Though its unclear how this was measured, this may explain the poorer nelfinavir performance.

Interpreting these data is difficult when the COMBINE team appear to have allowed ample opportunity for their study to be criticised. It's unhelpful that at the start of the study, more women and heterosexuals were recruited to the nelfinavir arm than to the nevirapine arm. It's possible that this failure to ensure that the two arms were well-matched may have biased the outcomes.

However, another possible explanation is that nelfinavir is less potent than nevirapine. In a small subset of 26 nelfinavir users and 21 nevirapine users who began treatment with viral load above 100,000 copies, a greater number of the latter had viral load below 50 copies after 36 weeks (15% versus 62% intent to treat analysis, 27% versus 62% on treatment analysis).

### Efavirenz versus nevirapine

Spanish researchers have presented preliminary information from the SENC study comparing efavirenz with nevirapine, both taken with ddI/d4T<sup>13</sup>. Over a 24 week period, the two treatments were found to be broadly comparable; around 80% had viral load below 50 copies at this point by intent to treat analysis. However, the sample sizes are very small; 28 in the nevirapine arm and 26 on efavirenz. In addition, participants began with fairly low viral loads, the median being just over 20,000 copies. For these reasons, it's very difficult to conclude from these data that these two NNRTIs are truly equivalent. Instead it may be wiser to wait the results of the 2NN study, ongoing in the UK, which compares these drugs with a dual NNRTI arm.

The SENC study does however provide some interesting information on side-effects. In both treatment groups, there were significant rises in total cholesterol levels over the study period. Efavirenz was observed to raise cholesterol in the efavirenz versus indinavir comparison study (DuPont's 006 study). However, this increase was due to a rise in HDL, or 'good' cholesterol rather than in LDL or 'bad' cholesterol.

The issue of side-effects may be the best way to choose between these two drugs in the absence of clear evidence on efficacy. There is little to choose between the two in terms of the simplicity of the regimen. Nevirapine is one tablet twice a day, efavirenz is three capsules once a day, and neither require restrictions on food or fluid intake.

Nevirapine's most significant side-effects are rash, which tends to appear early in treatment or not at all, and hepatitis, but the risk is low and nevirapine users must undergo regular liver function tests to monitor for this. There is some evidence that the risk of liver toxicity is higher in people who also have chronic hepatitis B or C infection.

Efavirenz's Achilles heel is the significant level of what are termed 'central nervous system (CNS) side-effects' – vivid dreams, euphoria, disorientation, etc. – associated with its use. According to a recent report from Australia, their persistence may have been underestimated<sup>14</sup>. 90% of 106 efavirenz users reported CNS effects in the early weeks of treatment, and these continued to occur during long-term follow-up in 40%. It seems many people persist with the efavirenz treatment nevertheless, reflecting the need to balance risks and benefits. Over an average follow-up of eighteen months, seventeen people stopped their efavirenz therapy due to CNS effects.

### Future NNRTIs

Capravirine, formerly known as AG1549, is an experimental NNRTI from Agouron which is being studied alongside nelfinavir, both taken with *Combivir*, in people new to treatment. This blinded study is recruiting in the UK. Capravirine is taken twice daily, and the side-effects which have been reported most frequently are nausea, vomiting and headache.

Emivirine, formerly MKC-442, is an NNRTI from Triangle Pharmaceuticals. It is not available in the UK at present. In combination with ddI/d4T in people new to treatment, it has reported rather disappointing results<sup>15</sup>.

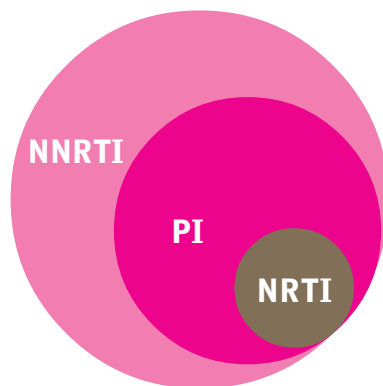
### Conclusions

There is evidence that both efavirenz and nevirapine are at least comparable to a single PI-based HAART regimen in people new to treatment. Whether one is a better choice for first-line therapy than the other is not presently known.

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### Changing anti-HIV therapy in English HIV clinics 1998-1999: What did people start with?

In 1998 and 1999, of 759 people who started first-line anti-HIV therapy, 50% started on one NNRTI and two NRTIs; 25% started on one PI and two NRTIs; and 4% started on three NRTIs or more drugs. The remainder began on two NRTIs.

Beck EJ. 5<sup>th</sup> International Congress on Drug Therapy in HIV Infection, abstract P68A, 2000.

# starting with NRTIs

Though other three NRTI regimens have been studied, the charge in this drug class has been led by the arrival of abacavir. Aside from its potency relative to other NRTIs, the other attraction of an abacavir-containing three drug NRTI regimen is that Glaxo Wellcome have co-formulated one regimen (abacavir/AZT/3TC) into one pill. This pill is called *Trizivir*, and is expected to be launched in the European Union in the near future.

Historically, abacavir/*Combivir* has been found comparable to indinavir/*Combivir* in the CNA 3005 study, though abacavir was found to perform less well in people who began treatment with high viral load (above 100,000 copies). This question around relative potency has hung over triple NRTI regimens, and they are not presently recommended for use in British treatment guidelines. This advice is to be reviewed over the coming months however,

and this process will take account of new data on abacavir.

## CNAA 3014

In the 3005 study, treatment allocation was blinded, which is likely to have removed any adherence advantage which abacavir/*Combivir* (two tablets twice daily) might gain over indinavir/*Combivir* (one tablet twice daily plus two tablets every eight hours) in real-world settings. This comparison was the subject of Glaxo Wellcome's CNAA 3014 study, which randomised 342 treatment naïve people to open-label use of one of these two regimens<sup>16</sup>. Just over one third of participants had viral load above 100,000 copies on entry.

In this preliminary 24-week report, viral load responses were comparable. By intent to treat analysis, 63% of abacavir users and 50% of indinavir users had viral load below 50 copies. In those who began with viral load over 100,000 copies, the figures were 55% and 45%. 21% of indinavir users, and 14% of abacavir users discontinued their study treatment, around 10% in each arm because of side-effects.

When participants were asked about their adherence, three quarters of abacavir users and just over half of the indinavir users reported having missed either zero or less than one dose of their medication per week. Whilst on the one hand this shows that adherence was better on abacavir, some argue that on the other hand, this doesn't compliment abacavir particularly well – relatively good adherence to abacavir appears to result in no greater efficacy than poorer adherence to indinavir.

## The Squirrel study

In the French Ecuireuil (Squirrel) study, abacavir/*Combivir* was compared to nelfinavir/*Combivir* in people new to treatment<sup>17</sup>. Nelfinavir was given three times daily. Just under 200 people were randomised to open-label treatment. Median viral load at entry

was just 20,000 copies, and few participants began with viral load over 100,000 copies.

Of 87 abacavir and 83 nelfinavir users who reached 24 weeks of treatment, 67% had viral load below 50 copies using an intent to treat analysis where people who switched treatment were considered to have failed. By the on treatment analysis, the proportions were 85% and 90%. 41% of nelfinavir users experienced diarrhoea, and the abacavir hypersensitivity reaction was seen in 4% of abacavir users.

## Conclusions

Overall, these studies provide fairly convincing evidence that abacavir/*Combivir* performs as well as a three times daily PI-based regimen in people who are new to treatment. Some will be looking for further follow-up on the issue of high viral load, and others may question whether abacavir/*Combivir* (and *Trizivir*, the single pill combination of abacavir/AZT/3TC) will prove to have an adherence/potency advantage over other twice daily regimens. Though *Trizivir's* one pill twice daily regimen is clearly a welcome advance in HIV therapy, it's worth remembering that nevirapine/*Combivir*, for example, adds up to two pills twice daily, efavirenz/*Combivir* is a daily total of five pills in two doses, and ABT-378/r/*Combivir* is four pills twice daily. Is there any good evidence that adherence is guided by pill burden at this level?

In addition there's been an appreciation of late that the NRTI class poses long-term toxicity risks, chiefly through damage to mitochondria within human cells. Though this area is not particularly well understood, the suggestion is that taking three NRTIs together may increase the risk. This is unproven.

There's concern too about the emergence of resistance mutations which produce multi-nucleoside analogue resistance in people who fail NRTIs. These are all unresolved questions for this drug class.

### analysing data

Intent to treat analysis is a method of analysing clinical trials where results from all participants enrolled in the trial are evaluated. An on treatment analysis considers results only from those who complete the trial. The former reflects the likely 'real-world' effects of a treatment; the latter the efficacy in people able to tolerate it.

### nucleotide RTIs

The first drug from this new class, adefovir, was withdrawn due to a high risk of kidney toxicity. Tenofovir appears not to be affected by this problem, and is a further alternative for first-line therapy. It is available in the UK through a blinded trial comparing it against d4T, with 3TC/efavirenz.

## starting with PIs continued

study comparing ritonavir/saquinavir with ritonavir/indinavir is due to report initial results mid-2001, and Glaxo Wellcome are studying amprenavir/ritonavir against other boosted PIs.

The combination of indinavir with ritonavir has been under investigation for some time. There is some evidence from the BEST study, which randomised people on three times daily indinavir (with nucleoside analogues) to either remain on that regimen or switch to 800mg twice daily indinavir with 100mg twice daily ritonavir, that tolerability worsens after the switch<sup>7</sup>. In this study there was more nausea in switchers (probably because of ritonavir), and more kidney stones (probably because of higher blood levels of indinavir).

The DIRECT study is a pilot study of indinavir/ritonavir (800/100mg) with 3TC/abacavir in treatment naïve individuals<sup>8</sup>. Median viral load at baseline, in the first 80 participants for whom results are available, was 102,000 copies, and median CD4 count was 275 cells. Using an on treatment analysis, 22 of 28 (79%) people who reached 24 weeks treatment had viral load below 50 copies.

Fifteen of 89 people enrolled developed flank pain, a pre-cursor of kidney stones, and three left the study for this reason. Overall, sixteen people have left the study, six for drug-related side-effects. 26 people had laboratory abnormalities, two had raised triglycerides and seven had raised cholesterol.

### Future PIs

The next generation of PIs includes Boehringer Ingelheim's tipranavir and Bristol-Myers Squibb's BMS-232632.

In the UK at present, the once daily BMS PI is only available through a blinded clinical trial. 24 week data from a dose-ranging study comparing the drug with three times daily nelfinavir, with ddI/d4T have been reported<sup>9</sup>. Participants were new to treatment, and underwent a two-week PI monotherapy period. After 24 weeks, the antiviral activity of the BMS PI appeared similar to nelfinavir. The most common side-effect in nelfinavir users was diarrhoea, and nausea in BMS-232632 users. Though cholesterol and triglyceride levels rose in the nelfinavir arm, they remained unchanged in the BMS-232632 arms. The BMS PI was associated with high levels of bilirubin (the pigment found in bile), however. This was severe in five cases, and seven people became jaundiced.

There is no access to tipranavir in the UK at present. Both of these PIs may have to undergo the same where-should-they-be-placed controversy which is currently dogging ABT-378/r. Tipranavir may benefit from a ritonavir baby-dose, as may Glaxo Wellcome's PI amprenavir, and perhaps allow both drugs to be dosed once daily<sup>10,11</sup>. Amprenavir recently became available on prescription in the European Union for use after a first PI. More detailed information on these products is available on our website, [aidsmap.com](http://aidsmap.com).

### Conclusions

Boosted PIs are a recent development which allow easier dosing of PIs, and – it seems – greater potency, but also potentially more toxicity. Because some boosted PIs may be effective in people with PI resistance it's unclear whether they may be best used as first-line therapy or later on, after other PIs have failed.

## L-acetyl carnitine for peripheral neuropathy

Peripheral neuropathy is a condition caused by nerve damage, which can occur during the course of HIV disease. Some anti-HIV medications, particularly nucleoside analogue drugs such as ddI, ddC and d4T can also cause peripheral neuropathy.

Recent studies have shown that a drug called LAC (L-Acetyl-Carnitine) can be effective in reducing pain and other symptoms associated with peripheral neuropathy, with few side-effects. Two studies investigating its use, one giving the drug intramuscularly, and the other orally, are recruiting participants with painful peripheral neuropathy, who have been on stable anti-HIV therapy for at least one month. Participating sites are in Manchester and London. Details on [aidsmap.com](http://aidsmap.com).

## Nandrolone & testosterone

This study is designed to study the effects of testosterone and the anabolic steroid nandrolone decanoate on lean body mass, body composition and body weight in men taking anti-HIV therapy. This five arm study involves a twelve week initial phase, followed by a two year maintenance phase. Treatment is blinded, but all arms will receive active injections of either steroid, or both, at some stage, and any participant who loses 5% or more of their

body weight during the maintenance phase will be offered intervention treatment. This trial is recruiting at the Kobler Clinic, London.

## NAM information forums 2001

There is no NAM Information Forum this month owing to the holiday period. However, dates for the first three meetings next year have now been set. On Monday, January 29<sup>th</sup>, the forum will look at the issues raised in this special issue of *AIDS Treatment Update* on the subject of *Which Anti-HIV Drugs First?*

The forum on Monday, February 26<sup>th</sup> will provide feedback from the 8<sup>th</sup> Conference on Retroviruses and Opportunistic Infections. This key scientific meeting, to be held in Chicago in early February, will be one of next year's most important HIV medical conferences. The NAM team will also be providing a live daily news service from this meeting for NAM's website [aidsmap.com](http://aidsmap.com). Visit [aidsmap.com](http://aidsmap.com) from February 4<sup>th</sup> to 8<sup>th</sup> to stay in touch with the latest news from the conference.

The March forum will be held on March 26<sup>th</sup>. The venue for these meetings is the University of London Union, Malet Street, London WC1, and they run from 7-9pm. Each month, we invite a leading HIV doctor to discuss a treatment-related topic, and answer questions from the audience. Entrance is free, a sign language interpreter is available, and everyone is welcome.

# news in brief



## 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 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 £9.95 to people with HIV, £57.50 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 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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