

AIDS TREATMENT UPDATE

MAY 1999

ISSUE 77

Combining two PIs

New information emerging on novel dual protease inhibitor combinations

BY ANNA POPPA

The latest advice from the British HIV Association (BHIVA), the UK professional body for doctors who care for people with HIV, has recently become available for consultation. The new draft guidelines include discussion of several new issues, one of which is the use of antiretroviral drug combinations which contain two protease inhibitors (PIs).

RATIONALE FOR COMBINING PIS

Though this is more true for some combinations than others, data on double PI regimens are limited at present and this is especially the case for their use in people who have some PI experience. Nevertheless, using PIs together rather than using the more standard PI/double nucleoside analogue regimens is an attractive prospect for several reasons:

- ♦ Interactions between PIs can alter the way individual drugs are processed through the body. This is particularly true for combinations including ritonavir, which inhibits an enzyme system in the liver resulting in slower metabolism of some other drugs. Doses of both drugs can then usually be lowered; it may be possible to take doses less frequently; and the effect of food on drug absorption might be less pronounced.
- ♦ Reduced dosing may lessen the initial side-effects which people starting a PI often encounter. (Though longer-term safety, and particularly the effects on fat metabolism are not known).
- ♦ Less complicated regimens may improve adherence, or at least prove less demanding.

The combination of ritonavir with indinavir is perhaps the best example of how this kind of drug interaction

can prove beneficial. There has been a lot of interest in this combination of late, and we review the latest research information in a special section overleaf.

NELFINAVIR WITH INDINAVIR

The combination of nelfinavir with indinavir has been less well studied. American researchers recently reported results from a dose-ranging study in 21 people, most of whom were new to treatment and 9 of whom had taken NRTIs before. Average viral load on entry was 50,500 copies. 1250mg nelfinavir twice daily dosed with 1200mg indinavir twice daily was selected as the optimal dose as this produced indinavir blood levels similar to those seen with the standard 800mg every eight hours dose. This suggests that the increased fluid intake mandated when indinavir is taken as a single PI remains important, (see ritonavir/indinavir section for more on this).

After 68 weeks of follow-up, 8 of the 21 had left the trial, most because of loss of viral control. Of the 13 remaining, 10 had viral load below 400 copies. 7 of these 13 had added NRTIs to augment their regimen. Though the treatment was described as

continued on page 3

Contents

Combining two PIs	1
Stopping prophylaxis	5
New UK trials	7
Glossary	8

Using ritonavir with indinavir

As a single PI, ritonavir is considered difficult to tolerate because of side-effects and its potential to interact negatively with many other drugs. Indinavir, on the other hand, must be taken at strict eight hour intervals, without food, and its tendency to cause kidney stones means those taking the drug must drink large volumes of fluid throughout the day.

Combining the two drugs reduces these drawbacks. It raises the trough level (the lowest level) to which indinavir falls in the period following a dose, and extends the time for which indinavir is present in the blood stream. In preliminary study the two drugs have therefore been taken twice daily and the need for indinavir to be taken on an empty stomach has been removed.

FLUID INTAKE

Whether the requirement to drink additional fluids with indinavir can be dropped is less clear, and may well be dependent on the dosages prescribed. When used in combination the two drugs have tended to be dosed either as 400mg ritonavir plus 400mg indinavir, or as 100mg ritonavir plus 800mg indinavir. (Either way these doses are to be taken twice a day).

The reason why people taking indinavir have been affected by kidney stones is because the drug deposits crystals in the kidneys when it passes through them. Drinking large amounts of fluids (about 1.5 litres a day) helps to flush out these crystals and reduces the risk of them forming kidney stones, or 'sludge' in the urine which makes urination painful. However, the formation of indinavir crystals in the first place is determined by the peak level which indinavir reaches soon after dosing.

Indinavir manufacturers Merck reported on the 100/800mg ritonavir/indinavir combination at the Sixth Retroviruses meeting in Chicago earlier this year. They found peak levels of indinavir to be raised by 30-50% compared to values reported in an earlier indinavir trial. A group of researchers from the Netherlands who studied the 100/800mg regimen in a larger group of 48 people did not observe an increase, however. Because of this lack of difference they concluded that "Patients should still drink at least 1.5 litres of fluid each day".

This advice appears unnecessary when both drugs are dosed at 400mg twice daily.

At last year's Geneva World AIDS Conference, Abbott presented data to show that indinavir peak levels were 62% lower using this dosing regimen than when indinavir is given three times daily as a single PI. According to an Australian study of the 400/400mg regimen this lowered peak level is associated with a lowered incidence of kidney stones. In this study, the 57 participants were instructed not to drink any extra liquid with their treatment, and whilst there is no control group of patients in the trial to compare outcomes against, there have been no cases of kidney stones or associated flank pain (pain in the lower back or sides) in 34 weeks of follow-up. (Kidney stones have been reported in between 3-15% of indinavir recipients in other trials).

Another concern about the 100/800mg regimen which arises from pharmacokinetic study (investigating how a drug is absorbed in the body), is that ritonavir trough levels may fall slightly lower than those required to inhibit HIV. It is speculated that this could allow drug resistance to develop if treatment does not fully suppress viral replication. Efficacy data on this regimen are not available to disprove or support this theory.

EFFECT ON VIRAL LOAD AND CD4

The Australian ritonavir/indinavir trial has reported efficacy data, albeit in rather a small groups of patients. 21 people, none of whom had taken anti-HIV treatments previously, began a four drug combination of ritonavir/indinavir (both dosed 400mg twice daily), along with the nucleoside analogues d4T and 3TC. Average viral load at baseline was 55,000 copies. Viral load was reduced to below 40 copies in 11 of 11 people treated for 48 weeks. In 7 participants followed for a year, the CD4 count had risen on average by 450 cells.

German researchers reported early viral load data on 84 treatment naïve recipients of ritonavir/indinavir (both dosed 400mg twice daily) taken with two nucleoside analogues. Median viral load at entry was rather high at around 240,000 copies. Of 43 people followed for 24 weeks, all had viral load below 500 copies, and 80% were below 80 copies. The most common side-effects reported were nausea (which caused four people to stop treatment), diarrhoea and tingling and numbness around the mouth (perioral paresthesia).

RITONAVIR LIQUID

Many of the dual PI combinations discussed in this article involve the use of ritonavir. Owing to a manufacturing problem, ritonavir is currently available in a liquid form which some users find unpalatable. The liquid will be replaced by a new soft gel capsule formulation in due course, but it remains unclear just how soon this will be.

See NAM Factsheet 27: *Ritonavir liquid* for tips on masking the taste, or speak to your doctor or pharmacist about injecting the liquid into gelatin capsules.

'well-tolerated', gastrointestinal side-effects were common, seen in 14 participants, though none discontinued for this reason. Kidney stones were seen in two people.

RITONAVIR WITH NELFINAVIR

The use of ritonavir with nelfinavir is another novel dual PI combination which allows twice daily dosing of both drugs. Researchers from the US Johns Hopkins group recently updated information on 20 PI naïve people, 10 of whom had experience of RTIs. All received 400mg ritonavir twice daily; 10 received 500mg nelfinavir twice daily and the other 10 received 750mg nelfinavir twice daily. Median baseline viral load was about 32,000 copies and CD4 count was 325.

Again, this combination was commonly associated with moderate to severe diarrhoea or nausea, though nobody stopped treatment for this reason. Most withdrawals were instead due to viral rebound. After week 12, participants had the option of adding NRTIs and most (12 of the remaining 15) chose to do so. Overall, 12 people had viral load which remained below 400 copies after 48 weeks treatment.

ABT-378 WITH RITONAVIR

ABT-378 is a new PI in development from Abbott. It can be taken with food, and is being developed as a twice daily drug, though once daily dosing also seems worth investigating. It is very sensitive to small amounts of Abbott's other PI, ritonavir – 50mg ritonavir boosts 400mg ABT-378 blood levels 77 times higher than when the drug is taken alone – a finding which has fuelled speculation that this dual PI combination may be active against some PI-resistant strains of HIV.

At the moment, however, there is no data on the use of this combination in people with PI experience, and little on people new to treatment. 24 week data from a dose-comparison study was reported in Chicago. 101 treatment naïve people were randomised to receive either 400/100mg of ABT-378/ritonavir, or 200/100mg, or 400/200mg. All participants received d4T/3TC as well. At entry, average viral load was around 70,000 copies. Ignoring four people who stopped treatment, 94% had viral load below 400 copies after 24 weeks. None of these discontinuations were due to side-effects; the most common of which were diarrhoea (18%) and loose stools (18%).

A Phase III study of this combination, for people who have not taken any other antiretrovirals is due to begin recruiting in

London and Brighton soon. Abbott do not plan to begin an ABT-378 expanded access scheme, which might bring the drug to people with more treatment experience, before the beginning of next year. They plan to manufacture the drug in a single capsule which contains both ABT-378 and ritonavir, and the dose will be three capsules twice daily.

Few studies have compared regimens containing a single PI with those containing two.

RITONAVIR WITH INVIRASE

Of all dual PI combinations, this one is the most well studied. The longest follow-up has come from a North American trial of 141 NRTI-experienced people. Median viral load on entry was around 40,000 copies, and after 12 weeks treatment participants could choose to add up to two new NRTIs; just 27 people did. Three quarters completed 48 weeks treatment, at which point 80% had viral load under 200 copies. At 60 weeks, 89 of 100 remaining participants had viral load below 200 copies, and 60 were below 50 copies. CD4 counts had risen on average by 176 cells. Side-effects such as diarrhoea, nausea and numbness around the mouth were common, and a total of 22 people withdrew due to adverse events.

This combination has also been studied in people who have already taken a single PI and this was the subject of an earlier article (see *AIDS Treatment Update* issue 69). In summary, these studies suggest ritonavir/saquinavir may be useful for some PI experienced people and not for others. People who have used nelfinavir as a first PI may do better than people who have used indinavir, and people who switch off a failing PI whilst their viral load remains low may have accumulated fewer resistance mutations which will give a better chance of being sensitive to a second PI.

NELFINAVIR WITH FORTOVASE

This is another relatively well-studied combination; the longest follow-up comes

ABT-378 STUDY

A new study which will compare the safety and potency of ABT-378/ritonavir versus nelfinavir in combination with d4T and 3TC in people who have not taken any HIV treatments is due to begin soon. Allocation to the different treatments will be blinded which means that neither participants nor their doctors will know who has been assigned which combination. Trials sites are at the Royal Free Hospital, the Chelsea and Westminster Hospital, St Mary's Hospital and the Royal Sussex County Hospital.

from the SPICE study. 157 PI naïve people, half of whom were NRTI naïve too, were randomised to receive either nelfinavir/2 NRTIs; *Fortovase*/2 NRTIs; nelfinavir/*Fortovase*/2 NRTIs; or nelfinavir/*Fortovase*. Average viral load on entry was 63,100 copies. At 16 weeks those who had a poor viral load response were allowed to switch to the four drug arm. After 72 weeks follow-up, using an intent to treat analysis (which includes data from all participants regardless of whether they stopped their trial treatment part way through), proportions with viral load below 50 copies are 35%; 35%; 51%; 22% respectively. The superiority of the four drug arm was also seen in the sub-group of treatment experienced people. Diarrhoea, nausea and vomiting were the most common side-effects.

The ongoing TIDBID study (see *AIDS Treatment Update* issue 71) is comparing nelfinavir/saquinavir dosed three times daily (as administered in the SPICE study) with a twice daily regimen. Data to 32 weeks suggest both regimens are equally effective in lowering viral load.

AMPRENAVIR COMBINATIONS

Glaxo Wellcome's experimental PI, amprenavir received accelerated approval in the US recently. It is available in the UK through clinical trials and an expanded access scheme. A very small study has reported preliminary information on dual combinations of amprenavir with either *Fortovase*, indinavir or nelfinavir. The main outcome was a lack of difference in effect on viral load between these three arms at 48 weeks. Amprenavir was dosed as 750mg three times a day – a total of 15 capsules. Adding the other PI gives daily totals of 27, 21 and 24 capsules respectively, and in this respect amprenavir/PI regimens do not compete well with most alternatives.

TWO PIS BETTER THAN ONE?

Few studies have compared regimens containing a single PI with those containing two. In the SPICE study, those who received nelfinavir/*Fortovase* with two NRTIs sustained undetectable viral load for longer than those who received either of those PIs with the two NRTIs. This was also true for participants who began with viral load over 100,000 copies.

A trial recently published in the journal *AIDS* compared combinations of two NRTIs with either indinavir, ritonavir or ritonavir/saquinavir in 284 people, 58% of whom had NRTI experience. At entry, average viral load was 50,000 copies. After 24 weeks there was no difference in the proportion of participants achieving viral load below 200 or 20 copies

overall. However, amongst participants who had not taken antiretrovirals before, viral load suppression was better in those receiving ritonavir/saquinavir. Significantly more patients in the ritonavir group (37%) stopped treatment because of side-effects than in the indinavir group (8%) or the ritonavir/saquinavir group (16%).

The Belgian IRIS Study found ritonavir/saquinavir/NRTI and indinavir/2 NRTIs to be equally potent in a group of 157 PI naïve people followed for 48 weeks. Median viral load at baseline was 100,000 copies and a third had taken NRTIs previously. There were, however, more discontinuations in the ritonavir/saquinavir arm (22) than in the indinavir arm (8).

Key conclusions:

- ◆ A range of dual PI combinations are being used to treat HIV. Ritonavir/saquinavir and saquinavir/nelfinavir have been most commonly used but new information is emerging on ritonavir/indinavir, nelfinavir/indinavir, ritonavir/nelfinavir and ABT-378/ritonavir.
- ◆ Combinations containing two PIs may be attractive to people who want to change a failing first-line 'protease-sparing' combination, and to those who cannot tolerate NNRTIs or NRTIs.
- ◆ Understanding of the use of these combinations by people who have already used a single PI is poor.
- ◆ There is some evidence that combinations containing two PIs may be more likely to suppress viral load than single PI-containing combinations, particularly for those who start treatment when their viral load is high.
- ◆ The long-term safety of dual PI combinations is not known. Early reports of changed fat metabolism amongst PI users suggested this side-effect may be more common in people receiving ritonavir/saquinavir than single PIs, but information on this issue is inadequate – few clinical trials of dual PI combinations have reported reliable information about lipid levels.

REFERENCES

- Following abstracts from 6th Conference on Retroviruses and Opportunistic Infections, Chicago, 1999: Saah 362, Burger 363, Workman 677, Rockstroh 631, Squires 364, Gallant 393, Murphy 15, Johnson 389, Slater 390, Florence 630. From 12th World AIDS Conference, Geneva, 1998: Hsu 22361. From 4th International Congress on Drug Therapy in HIV Infection, Glasgow, 1998: Eron, 84. Also: Sham HL et al. *Antimicrobial Agents and Chemotherapy* 42:3218-3224, 1998; Cameron DW et al. *AIDS* 13:213-224, 1999; Kirk et al. *AIDS* 13:F9-F16, 1999.

Stopping prophylaxis

Does a good response to antiretrovirals mean the end of preventive therapy?

BY KEITH ALCORN

Until very recently people who had experienced a number of AIDS-related illnesses needed to take medication for life to prevent recurrences of those illnesses. This is called secondary prophylaxis, or maintenance therapy. In addition, when the CD4 count went below a certain level, preventive treatments (primary prophylaxis) were recommended.

In the past couple of years HAART has changed the accepted wisdom about what forms of prophylaxis might be necessary. This is because many people who have had AIDS-related illnesses have enjoyed CD4 rises that might be expected to take them out of the danger zone for developing opportunistic infections and cancers.

PCP

Prophylaxis against PCP was previously recommended in people with CD4 counts below 200-250. Prophylaxis usually consists of co-trimoxazole (*Seprin*) either once daily or three times a week. Co-trimoxazole has no significant drug interactions with anti-HIV drugs, except for 3TC.

A Dutch study of 62 people on HAART who stopped primary PCP prophylaxis and 16 who stopped PCP maintenance therapy after their CD4 count rose above 200, reported that none developed PCP during 12 months of follow-up. The average lowest level to which CD4 fell in this group before treatment was 79 cells. When PCP prophylaxis was stopped the average CD4 count was 347 cells.

A similar study of 196 patients from Switzerland with CD4 counts which had risen above 200 after HAART found no cases of PCP after an average of 7 months follow-up. However, these are relatively short periods of follow-up, and some doctors continue to warn against drawing firm conclusions.

A more recent, large-scale study suggests some people do remain at risk. 626 people on HAART with a previous CD4 count below 200 whose CD4 count rose over 200 on treatment (Group 1), were compared with 3,497 people who had never had a CD4 count below 200 (Group 2). Group 1 had either never started or had stopped PCP prophylaxis. Analysis found no difference in the incidence of PCP between the two groups. However, researchers suggested that among people whose CD4 counts had been below 25, there was a trend towards a greater risk of PCP, even after a subsequent CD4 cell

increase, and advised caution around discontinuation in these circumstances.

Another recently published study reported information on 378 people who stopped PCP prophylaxis after an average of ten months on HAART. 319 of these had never had a bout of PCP before. The average lowest CD4 count in this sub-group was 123 cells, compared with 60 cells in the group of 59 people who were on maintenance therapy. Prophylaxis was stopped when the CD4 count had risen to 270 cells (the same for both groups), and had been taken for an average of 16 months. CD4 counts had been sustained above 200 for an average of 8 months before prophylaxis was stopped in the primary prophylaxis group, and 5 months in the secondary group. Over a follow-up period of 7 months off prophylaxis in the primary group; 5 in the secondary, there were no cases of PCP.

The authors suggest that the risk posed by stopping PCP prophylaxis after a sustained increase in CD4 above 200 is sufficiently low in people who have never had PCP to warrant discontinuation. They advocate further study before such guidance can be offered to people taking secondary prophylaxis.

In the UK, doctors report that many people who have sustained their CD4 counts above 250 are stopping prophylaxis. The Medical Research Council is collecting data on the effects of ceasing PCP prophylaxis.

CMV

Diagnosis of CMV disease prior to HAART always signalled the need for lifelong treatment. Although treatments for CMV retinitis and systemic CMV (throughout the body) have become easier to take, the drugs used in secondary prophylaxis, and the procedures required to deliver them, are still toxic and uncomfortable for many people. On the other hand, each CMV retinitis relapse results in a permanent patch of lost vision, and increases the risk of detachment of the retina, which further threatens sight.

Secondary prophylaxis usually consists of oral ganciclovir treatment, with the possibility of injections into the eyeball once monthly or the implant of a small bead which delivers ganciclovir to the eye in cases where retinitis has only affected one eye. If CMV has affected both eyes, or if it has previously caused disease in other organs such as the gut, oral ganciclovir treatment will be necessary.

COTOX

The COTOX study compares different ways of managing people who stop co-trimoxazole (*Seprin*) prophylaxis for PCP because of side-effects, but are considered still to need PCP prophylaxis. People with a mild or moderate (not severe) reaction to the drug will be invited to choose between stopping or continuing treatment. Those who elect to stop (or who have stopped in the past) will be allocated at random to either de-sensitisation (restart the drug at gradually increased doses), or re-challenge (restart on the normal dose immediately). COTOX is recruiting at sites in London, Brighton, Peterborough, Sheffield, Birmingham and Liverpool.

There is some evidence that HAART is preventing the progression and recurrence of CMV disease. One group of eight HAART recipients in San Diego stopped CMV maintenance therapy and experienced no CMV relapses after an average of 146 days. Likewise, in Spain a group of seven people discontinued CMV maintenance yet experienced no CMV progression over 25 months. In the largest study to date, follow-up of 52 French patients who stopped CMV maintenance therapy after a median 18 months of HAART demonstrated one case of retinitis at a CD4 count of 300. CMV viraemia (the presence of CMV in the blood), was undetectable in this patient.

However, there have now been several reports in which people whose CD4 counts had fallen below 100, and subsequently increased substantially after HAART, developed a first episode of CMV disease at relatively high CD4 counts (e.g. 200 or above). Another group has reported that four out of five CMV reactivations occurred in the same part of the eye previously affected by CMV retinitis. These findings suggest that the immune restoration seen among people taking anti-HIV therapy may be insufficient to protect against CMV disease, at least in the early months, and an individual's risk of CMV disease may be best gauged from his or her lowest ever CD4 count rather than its current value. It is possible that in these cases CMV had already 'seeded' the eye before protease inhibitor therapy was started.

The risk of CMV reactivation appears to be determined by the degree of immune reconstitution (the ability of the immune system to control CMV on its own) and the presence of detectable CMV viraemia. Whilst some clinics may discuss the option of stopping CMV maintenance if sustained increases in CD4 count (e.g. above 100 or 200) are seen after taking HAART (especially if side-effects are a problem and the extent of previous retinitis is limited), others are also testing for CMV viral load and/or the strength of specific immune responses to CMV to provide further information. Researchers at the Royal Free Hospital, London, have reported that CMV antibody responses improved in a small group of people taking HAART. 10 out of 12 people lost any traces of CMV in their blood soon after starting HAART, and none developed CMV retinitis. 10 patients who received only NRTIs or no treatment at all were followed as a control group; 5 of them developed CMV disease after ten months follow-up.

In addition to CMV reactivations, there are case reports of a condition called cystoid macular oedema, which causes impaired vision and inflammation of the eye in people who had been successfully treated for CMV

retinitis. Cystoid macular oedema and other inflammatory complications have been attributed to the immune system, strengthened due to HAART, mounting an attack on CMV.

MAI

Anyone who experienced the bacterial infection MAI in the past was advised to take maintenance treatment, usually rifabutin and ethambutol, or azithromycin. Rifabutin is an awkward drug to prescribe with protease inhibitors because of drug interactions, so azithromycin is used more often nowadays.

MAI has become less common since the widespread use of HAART. However, people who have recently started PI treatment may be at risk of an unusual form of MAI, characterised by swollen lymph nodes and fever. These symptoms are thought to be caused by the recovering immune system over-reacting to low levels of MAI infection that were present before treatment began.

So far, research on stopping MAI prophylaxis has involved few participants. A UK study of 13 people with two consecutive CD4 counts over 50 who stopped MAI prophylaxis, found no cases of MAI after a median follow-up of 231 days.

Dr Anton Pozniak, of London's Chelsea and Westminster Hospital advises that people who have been taking MAI secondary prophylaxis can consider stopping after three successive blood tests for MAI have proved negative, and the CD4 count has remained above 100 for at least three months. However, this approach is not shared by all members of NAM's Medical Advisory Panel, some of whom strongly caution against stopping MAI prophylaxis whilst there are no data from large, long-term comparative studies to confirm the safety of doing so. In the meantime, guidelines recommend that decisions about prophylaxis should be based on your lowest ever CD4 count, not its current value.

OTHER COMMON INFECTIONS

- ◆ **Candidiasis:** Protease inhibitor treatment has been associated with a substantial fall in the incidence of candida, and prophylaxis is rarely required.
- ◆ **Cryptococcal meningitis:** 200mg fluconazole daily is the recommended maintenance treatment; people with CD4 below 100 are at risk.
- ◆ **Toxoplasmosis:** Co-trimoxazole (used to prevent PCP) also prevents toxoplasmosis.
- ◆ **Herpes:** Acyclovir maintenance to prevent recurrences of genital herpes, severe oral herpes and gastrointestinal herpes is still routinely prescribed.

REFERENCES

- From 4th Conference on Retroviruses & Opportunistic Infections (CROI), 1997: Gilquin 354.
From 37th ICAAC, 1997: Torriani I-33, Tural I-36.
From 4th Annual BHIVA meeting, 1998: O'Moore 6, Gill P9.
From 12th World AIDS Conference, 1998: Furrer 22180.
From 6th CROI, 1999: Dworkin 392, Joan 456, Torriani 250.
From 5th Annual BHIVA meeting, 1999: Deayton 022.
Jacobson MA et al. *Lancet* 349:1443-1445, 1997.
Aberg JA et al. *Journal of Infectious Diseases* 178:1446-1449, 1998.
Schneider MME et al. *Lancet* 353:201-203, 1999.
Weverling GJ et al. *Lancet* 353:1293-1298, 1999.

NEW UK TRIALS

INITIO

INITIO is one of several new trials run by the Medical Research Council (MRC). This large study, which will include a total of 1,070 participants in centres around the world, will compare the pros and cons of starting treatment with either an NNRTI-based regimen, a protease inhibitor (PI)-based regimen, or a regimen containing both an NNRTI and a PI. In the second stage of INITIO, those whose first combination fails will change to a new regimen where the dual NRTI backbone is switched to three new NRTIs and the NNRTI is replaced with a PI (or vice versa). Those who began with an NNRTI plus a PI will switch to the three new NRTIs and two new PIs.

Participants will be followed for at least three years, by which time investigators hope to know more about which first-line regimens fail less often, which are more tolerable, which are easier to adhere to, and how developing resistance impacts on future treatment options.

100-150 people who have not taken any anti-HIV treatments before will be recruited to INITIO through sites across the UK and in Ireland. Allocation of treatment will be at random. All will receive ddI/d4T plus either efavirenz, nelfinavir or both.

FORTE

Another MRC trial, FORTE replaces an earlier study called ProCom. FORTE will investigate whether anti-HIV therapy which begins with an induction period with four drugs, followed by maintenance with three, is more effective than the more common approach of beginning treatment with three drugs. This strategy, sometimes called 'de-intensification' has so far proved unsuccessful in other studies, (see *AIDS Treatment Update* 72, 63).

It is suggested that an important factor in the failure of most other induction-maintenance trials has been the de-intensification from three drugs to two, and in most cases to two NRTIs – generally considered inadequate therapy these days. FORTE differs from this model. Participants will begin treatment with either a four drug combination of ddI/d4T/nevirapine/nelfinavir, or a three drug combination of ddI/d4T/nevirapine. After 24 weeks, a proportion of those in the four drug group will switch down to three drugs by stopping nelfinavir. Participants will only be eligible for de-intensification if their viral load is below 50 copies in two consecutive tests.

FORTE aims to recruit 150 participants, all of whom should not have taken anti-HIV treatment before. Again, participating sites are in London and across the UK.

Maintaining 3TC

Resistance to 3TC develops easily if you have any detectable level of HIV in your blood whilst taking the drug. However, it has been suggested that – unlike the case of other antiretrovirals – 3TC resistance may have some benefit. The Colate study will investigate whether people who do not achieve or sustain undetectable viral load whilst taking a first-line 3TC-containing combination are better off discontinuing 3TC or maintaining it within their second-line combination.

This is an open-label study for people with viral load above 10,000 copies on their first combination (which must include 3TC and at least two other drugs). Participants will be randomised to continue or stop 3TC within their second combination (which will contain a PI and at least three drugs in all). Recruitment begins soon at the Royal Free and St Mary's (London) and the Royal Sussex (Brighton).

Abacavir v PI

The Royal Free Hospital will shortly begin recruiting participants to an open-label trial which will compare abacavir with a PI in people who are also taking two NRTIs. The trial is open to people who have been stable on a first-line, three drug combination containing a PI and two NRTIs for at least six months. Participants will continue their NRTIs and be randomised either to switch the PI for abacavir or to remain on the PI.

Thalidomide & lipids

Thalidomide has been used experimentally to treat a number of conditions in which the immune system seems to attack the body's own cells. It has also been suggested that it might encourage weight gain.

Participants in study PK-UK008 will be randomised to receive thalidomide or placebo in addition to their existing PI-containing therapy. The trial will evaluate the effect of thalidomide on viral load and study the interaction between thalidomide and PIs. It will also investigate thalidomide's effect on lipid metabolism, which can become altered in people taking PIs. This study is currently recruiting at the Royal Free and in Brighton.

TRIALS INFO

Details of current UK clinical trials can be found in NAM's *HIV & AIDS Treatments Directory*, (fully updated Sixteenth Edition out this month), available from NAM and in most AIDS Service Organisations. Participating sites for INITIO and FORTE were still being finalised at the time of going to press, but will be available soon on the NAM/BHIVA website aidsmap.com.

NAM FORUM

Making More of Anti-HIV Treatment is the subject of May 24th's Forum, which will feature the latest information on combining PIs, using hydroxyurea, and immune boosters. Venue: Room 3E, 3rd Floor, University of London Union, Malet Street, London W1. Time: 7-9pm.

ABACAVIR NEWS

Glaxo Wellcome's abacavir has been recommended for accelerated approval in the EU and should become available on prescription within several weeks.

GLOSSARY OF TERMS

antiretroviral Something that attacks retroviruses such as HIV

CD4 Molecule on the surface of some cells onto which HIV binds. CD4 cell count roughly reflects the state of the immune system

cross resistance When resistance to one drug reduces the virological response to subsequent treatment with another drug which has not been taken before

expanded access scheme A programme which allows access to an experimental drug outside clinical trials for people in need

gastrointestinal Relating to the body's digestive system

HAART Highly Active Antiretroviral Therapy, potent combination therapy, usually including a protease inhibitor

lipid A general term for fats in the blood

metabolism Mechanisms which sustain life, including turning sugar and fat into energy

naive Never having taken anti-HIV treatments before

NNRTI Non-nucleoside reverse transcriptase inhibitors: anti-HIV drugs that include nevirapine, delavirdine, and efavirenz

NRTI Nucleoside analogue reverse transcriptase inhibitors: anti-HIV drugs that include AZT, ddI, ddC, 3TC and d4T

PCP Form of pneumonia seen in people with

low CD4 counts

protease An enzyme that HIV uses to break up large viral proteins into smaller ones

protease inhibitor Anti-HIV drugs which target the protease enzyme, e.g. saquinavir, ritonavir, indinavir, nelfinavir

randomisation Process of selecting by chance treatment a trial participant will receive

regimen Drug or treatment combination

resistance A drug-resistant HIV strain is less susceptible to the effects of one or more anti-HIV drugs because of its genetic make-up

resistance mutation A change to HIV's genetic structure which confers resistance to an anti-HIV drug

reverse transcriptase An enzyme which converts genetic material from RNA into DNA, an essential step in the lifecycle of HIV

RTI Reverse transcriptase inhibitor

steroids Immune-suppressing drugs used to damp down excessive immune responses

undetectable viral load A level of viral load that is too low to be picked up by the particular viral load test used

viral load The amount of virus in a sample. HIV viral load indicates the rate at which HIV is reproducing in the body

virologic response Effect of treatment on viral load

AIDS TREATMENT UPDATE

Published monthly by



NAM Publications
16a Clapham Common
Southside
London SW4 7AB
Tel: 0171 627 3200
Fax: 0171 627 3101
E-mail: atu@nam.org.uk

<http://www.aidsmap.com>

Editor:
Anna Poppa

AIDS Treatment Update
founded by Peter Scott
Copyright: © NAM
Publications 1999
All rights reserved

Design:
Positive Design Works,
London W10

Imagesetting & Printing:
Cambrian Printers,
Aberystwyth

ISSN: 0969-4706

Subscriptions

Free to individuals in the UK affected by HIV or AIDS. Professional/organisational rate: £69/year. Voluntary organisation rate: £50/year. Overseas rate: within EU add £10/year; outside EU add £15/year. Tel: Helen or Letitia on 0171 627 3200

Medical Advisory Panel

Dr Fiona Boag, Dr Ray Brettell, Professor Janet Darbyshire, Dr Martin Fisher, Professor Brian Gazzard, Dr Diana Gibb, Professor Frances Gotch, Professor Paul Griffiths, Dr Margaret Johnson, Dr Jacqueline Mok, Dr Graeme Moyle, Professor Tony Pinching, Dr Gareth Tudor-Williams, Professor Jonathan Weber, Dr Ian Williams, Dr Mike Youle

Thanks to our funders

NAM's treatments education for people living with HIV is provided free thanks to the generosity of: The Department of Health, the Inner London HIV Health Commissioners Group, Levi Strauss & Co, Glaxo Wellcome UK, Crusaid, Bristol-Myers Squibb, Boehringer Ingelheim, Roche Products, Pharmacia & Upjohn, Du Pont Pharma, Merck Sharpe & Dohme, Enfield & Haringey Health Authority, Abbott Laboratories, Barnet Health Authority, Redbridge & Waltham Forest Health Authority, Bexley & Greenwich Health Authority.

ANY QUESTIONS?

The following national agencies, all based in London, offer one-to-one advice and information about treatment options, in person or over the telephone:

♦ AIDS Treatment Project

Phoneline: 0645 470047
Monday & Wednesday, 6pm - 9pm
All calls charged at local rates.

♦ Body Positive

Treatment Advice: Tue, Wed & Fri 2pm - 7pm
Call Adam, Jo or Robert on 0171 287 8010 to make an appointment.

♦ The Terrence Higgins Trust

Helpline: 0171 242 1010 Daily 12noon - 10pm
Treatment Support: Call Sarah Porch on 0171 831 0330 for an appointment.

NAM recommends readers to seek treatment advice from more than one source, and to discuss all your decisions with your doctor.

The publishers have taken all such care as they consider reasonable in preparing this newsletter. But they will not be held responsible for any inaccuracies or mis-statements of fact contained herein. 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.

Donations towards production costs are welcomed.