

aids treatment update

changing times in HIV medicine

For many of us the New Year is a time of looking forward and thinking about change. That's very much the theme of this month's *ATU*. In our lead article this month, we review two new candidates in the HIV drug pipeline, atazanavir and fos-amprenavir. Experimental HIV treatments are always of interest to *ATU* readers, but particularly these drugs because they're amongst the new generation within the protease inhibitor class, where the change we're all hoping for involves a desire to retain antiretroviral potency, whilst improving tolerability.

We also look this month at adherence to HIV therapy; taking medication as it was prescribed, a subject of fundamental importance to treatment success, and yet one which arguably continues not to receive the attention it deserves. At NAM's website aidsmap.com, practice guidelines on HIV treatment adherence, which aim to lay down a blueprint for the ways in which people prescribed HAART should be supported, are now open for consultation. When presenting these recommendations at a recent international HIV conference, Israeli physician Jonathan Shapiro acknowledged that their implications for HIV care are significant. This is an area where in 2003 we need to hear more from some of the louder voices in the field. Urging his fellow professionals to take up the adherence challenge, Jonathan's message was clear: "What's needed is a change of attitude."

NAM wishes all our readers, and your families and friends, a happy and healthy New Year.

new protease inhibitors 2

adherence:
elements of success 7

news in brief 10

new protease inhibitors

2 a look forward to the next generation of HIV drugs by anna poppa

If my memory serves me correctly, it was at an HIV resistance meeting in Arizona in June 2001 that Dr John Mellors, a well-known American researcher rather closely allied to the 'Hit Hard Hit Early' approach to HIV medicine, predicted that protease inhibitors, a drug class rather down on its luck, would resurface, phoenix-like, before long.

Once the stalwarts of triple drug HIV therapy, the old-school protease inhibitors (PIs); indinavir, ritonavir, saquinavir and nelfinavir, have gradually been eclipsed by newer models which appear to offer comparable efficacy but greater tolerability. The response of PI manufacturers to calls for less demanding regimens was to focus on some rather clever pharmacology; using drug interactions to deliver regimens with lower pill burdens and enhance antiviral activity.

These boosted PIs have not been a complete success, however. Concerns about their effects on fat and sugar metabolism remain. Lopinavir/ritonavir (*Kaletra*) for example, whilst highly potent against both wild-type HIV, and HIV which is resistant to some PIs, is associated with similar increases in triglycerides and cholesterol to those seen with older drugs in this class. Whilst valued for its drug-boosting properties, the cost of including ritonavir in any drug regimen may prove too high for some people. A recent report from the DAD cohort, set up to track the long-term safety of antiretroviral therapies, found that people taking ritonavir-containing HAART regimens, including dual PI regimens, had worse blood lipid profiles than those on other PIs¹.

Clearly for PI manufacturers, compact regimens may not be enough to win back market share. Instead, what's needed are PIs which do not raise

the pulse of cardiologists – to use the current terminology, PIs which are 'metabolically clean'.

Atazanavir

Atazanavir is an experimental PI in Phase III development by Bristol-Myers Squibb (BMS). Formerly known as BMS-232632, it is being positioned by BMS as the first once daily PI. Taken as a single PI, it is dosed as two 200mg capsules per day with food.

Atazanavir has been compared with nelfinavir in a randomised controlled trial involving people new to HIV treatment, study AI424-008. This trial found no difference between the two drugs (which were taken with d4T/3TC) in terms of effect on viral load or CD4 after 48 weeks. Treatment with nelfinavir was associated with an increase in total cholesterol, LDL cholesterol and triglyceride levels. However, these values did not change significantly amongst atazanavir recipients, and it's been this promise of an improved metabolic profile which has raised most interest in this drug².

Atazanavir has also been investigated in people with prior experience of taking PIs. Nelfinavir recipients in study AI424-008 have been switched to atazanavir and rolled over into an observational follow-up study. Initial data from these individuals were reported in the summer of 2002. After twelve weeks on atazanavir, average lipid levels in the 63 people switching their PI were improved³.

A further study (BMS-009) randomised people taking a failing PI regimen to a new regimen including either atazanavir/saquinavir or ritonavir/saquinavir. Viral load reductions were comparable after 48 weeks treatment. Lipid levels were stable amongst atazanavir

recipients, but rose amongst those taking ritonavir⁴. (These three studies were reviewed in *ATU* issues 109 and 117).

Atazanavir versus efavirenz

More recently, BMS have reported data from a study comparing their PI with the market-leading NNRTI, efavirenz (also a BMS drug) in people new to treatment. For many observers, study AI424-034, provides a sterner test for atazanavir than the earlier nelfinavir comparison trial. Recent data have made a strong case for the use of efavirenz/AZT/3TC as the first-line regimen of choice in HIV infection (see *ATU* issue 116). Rather than their own NRTIs, ddI and d4T, BMS selected AZT/3TC as the NRTI backbone in study 034, ensuring the trial's findings have direct relevance to current clinical practice. Further, because both efavirenz and atazanavir are dosed once daily, it's more difficult to argue that any variations in efficacy may be the result of regimen-related adherence differences.

Study 034 randomised 810 treatment naïve individuals to receive 48 weeks of treatment with either atazanavir (400mg once daily) or efavirenz (600mg once daily). Allocation of these drugs was blinded by placebo, and everyone also received AZT and 3TC dosed twice daily. The trial was open to people with viral load above 2,000 copies and CD4 counts above 100 cells (or 75 cells for people with no prior AIDS-defining illnesses)⁵.

At entry, median viral load was 4.88 log copies, with 42% having a value over 100,000 copies (5 logs). Median CD4 was 282 cells. After 48 weeks there were no differences between arms in the proportions with viral load below 400 copies (70% atazanavir and 64% efavirenz respectively), or below 50 copies (32% versus 37%). CD4 increases were also similar. Results were analysed on an intent-to-treat basis, where those who switched any drug in their regimen were considered to have experienced treatment failure.

In comparison to other studies, the virological responses in this trial appear quite poor for first-line therapy, particularly the numbers reaching the below 50 copy target. The trial design required that anyone whose viral load rebounded above 50 copies on two sequential

occasions would be considered to have a viral load above 50, even if their viral load subsequently returned below this cut-off by 48 weeks. This stipulation may have contributed to the poor virological data because, for example, anyone experiencing blips in their viral load would be considered to have failed treatment, (along with those switching drugs for toxicity).

Similar numbers stopped treatment early in each arm; 18% overall, and 7% for side-effects. Mild to severe side-effects considered to be related to the study drug occurred in just over 40% of participants in each arm, the most common being nausea. Whilst rash and dizziness were more frequent for efavirenz users, jaundice and scleral icterus (yellowing of the eyes) were more common in the atazanavir arm. Whilst none of these were unexpected problems, the latter remains something of a concern.

Atazanavir's major side-effect is a tendency to raise levels of bilirubin in the body, a pigment found in bile. Bile is produced by the liver as an aid to digestion, and whilst increases in bilirubin are not harmful, the symptoms which may result (yellowing of the skin and eyes) are likely to be considered undesirable by many people. In study 034, whilst 33% of atazanavir users experienced an increase in bilirubin, jaundice or scleral icterus were observed in 6%. Five per cent of atazanavir users overall required a dose reduction because of raised bilirubin, and less than 1% stopped treatment. BMS argue that dose reduction effectively controls the jaundice and enables atazanavir to be maintained. Few data have been presented on this issue, however, and so questions remain about the efficacy of a lower dose.

Study 034 supports earlier data regarding atazanavir's effects on lipid and sugar processing. Atazanavir treatment resulted in either no change or a decrease in fasting total cholesterol, fasting LDL cholesterol and fasting triglycerides, and an increase in fasting HDL cholesterol. Whilst efavirenz produced increases in these parameters, 48 week values remained within 'desirable' ranges according to US guidelines on cholesterol changes (known as the National Cholesterol Education Program Guidelines). Average glucose and insulin levels remained similar to baseline in both groups.

TMC114

TMC114 is an experimental PI in development by Tibotec-Virco, now part of Johnson & Johnson. A dose-ranging study is currently recruiting volunteers at the Royal Free Hospital, and at the Chelsea and Westminster Hospital, London. Entry is open to people who have previously used between two and four PIs, and have viral load above 5,000 copies on their current regimen. Participants will be randomised to remain on their current HAART regimen, or to replace their current PI with one of four TMC114 regimens. More details are available on aidsmap.com.



new protease inhibitors continued

Resistance and drug interactions

The mutation which has been most closely linked to atazanavir resistance in studies so far is I50L, a mutation not associated with resistance to other PIs. However, the significance of acquiring this mutation may vary according to prior experience of PIs and the presence of other PI resistance mutations. Those whose PI use is limited to atazanavir may be expected to benefit from other PIs despite the presence of I50L. People who have taken other PIs before atazanavir, may find that the I50L mutation contributes to broad resistance to drugs in this class⁶. The N88S mutation is also seen in people with resistance to atazanavir, and this may be expected to result in some cross-resistance with other PIs.

The impact of drug interactions is also under investigation in relation to atazanavir. The tablet version of ddI is known to reduce atazanavir levels, as does efavirenz. Preliminary data suggest that adding 200mg of ritonavir 'corrects' the efavirenz interaction by raising atazanavir levels significantly. Whether this will prove an attractive strategy is not yet clear – those considering atazanavir for its seemingly improved metabolic profile may wonder if this benefit will be lost if ritonavir is included in their regimen. At present this area involves much guesswork however, as there are no data on the clinical effects of this combination in people with HIV.

As noted earlier, the dual PI combination of atazanavir with saquinavir has been evaluated in people with prior experience of PIs, and so is a little better understood than other atazanavir/PI options. Once daily dosing is possible, and two different regimens were found effective in reducing viral load by more than one log after 48 weeks – 1200mg saquinavir with either 400mg or 600mg atazanavir. PIs were given with two NRTIs in this study.

Access to atazanavir

BMS have submitted applications for approval of atazanavir in both the European Union and the USA. At present in the UK, the drug is available through participation in a clinical trial aimed at people who have used two or more PIs already.

Late last year, the company opened an early access programme at twenty UK treatment centres. To be eligible for this programme, a person must be failing on their current HAART regimen (defined as a viral load above 5,000 copies and a CD4 count below 300 cells) and need atazanavir in order to construct a viable alternative treatment regimen.

Atazanavir is also available via this scheme to people who have HAART-associated increased lipids which have not responded to lipid-lowering drugs. Viral load and CD4 restriction criteria do not apply for this group. The access programme does not allow atazanavir to be added to failing regimens as a single drug, and advises that it should not be used with lopinavir/ritonavir. (Full details of the scheme are available at aidsmap.com).

BMS also plans a study of switching to atazanavir for people who have experienced lipid elevations on their first protease inhibitor; lipid elevations must not have responded to standard lipid-lowering drugs. This study will recruit twenty people in the UK.

Fos-amprenavir

Amprenavir is a licensed PI manufactured by GlaxoSmithKline (GSK) and sold under the tradename *Agenerase*. Because of its high pill burden when taken as a single PI, and some unimpressive trial results in people new to treatment, the drug has never been a particularly popular choice. Indeed within the European Union, the drug is licensed for use in people with prior experience of other

antiretrovirals only. The addition of a ritonavir boost improves response to amprenavir, and in the USA, two amprenavir/ritonavir combinations are approved for use: 1200mg/200mg once daily or 600mg/100mg twice daily.

For some time GSK have been working on a new version of amprenavir, and early data on this drug are now being reported. Fos-amprenavir (formerly known as GW-433908) is an amprenavir pro-drug, which means that it is converted to amprenavir inside the body. This re-formulation reduces the pill burden, and raises blood levels. Taking the drug with ritonavir allows both to be dosed once daily.

NEAT (APV30001) is a GSK-sponsored study comparing fos-amprenavir with nelfinavir in people new to HIV treatment. Preliminary 24 week results were reported at the 42nd ICAAC in San Diego last year⁷. NEAT randomised 249 people (2:1) to receive open-label fos-amprenavir (1400mg twice daily) or nelfinavir (1250mg twice daily), plus twice daily abacavir/3TC. Median viral load at entry was 4.8 log copies and median CD4 was 213. A little under half the trial population had viral load above 100,000 copies, and a similar proportion had CD4 counts below 200. This was therefore, a group with quite advanced disease, which is likely the result of opening the study to people with *any* CD4 count, and the fact that around 40% of participants were recruited from South Africa, Panama and Puerto Rico.

After 24 weeks, 73% of fos-amprenavir recipients, and 54% of nelfinavir recipients had viral load below 400 copies by intent-to-treat analysis, where subjects with missing values were considered to have experienced treatment failure (ITT M=F). Proportions reaching below 50 copies were 54% and 40% respectively. When the results were analysed according to viral load at entry, fos-amprenavir clearly out-performed nelfinavir in those with baseline values above 100,000 (71% versus 35% below 400 copies, and 42% versus 11% below 50 copies). Responses in those with lower viral load levels were comparable between arms. CD4 responses were similar; a median increase of around 125 cells.

Twenty-eight per cent of nelfinavir users stopped their treatment before 24 weeks

compared to 19% of those on fos-amprenavir. The excess in the nelfinavir arm appeared to be the result of 'insufficient virological response', seen in nine (11%) of those who stopped nelfinavir early and four (2%) stopping fos-amprenavir early. It's important to bear in mind, however, that baseline viral load was high in this study.

There was no difference in the frequency of side-effects between arms overall. Mild to severe events occurred in 28% and 31% of participants, the only significant difference being the frequency of diarrhoea, which was more common amongst nelfinavir users. Serious side-effects were seen in 16% of trial participants, and caused treatment to be stopped in nine fos-amprenavir users (5%) and five nelfinavir users (6%). One discontinuation in each arm was due to abacavir hypersensitivity reaction.

In common with atazanavir, interest in any new PI is likely to focus as much on its effects on metabolic parameters as anything else. According to available data from the NEAT study, neither PI was associated with significant abnormalities in triglycerides, total, LDL or HDL cholesterol after 24 weeks.

Fos-amprenavir/ritonavir

A second GSK-sponsored trial, the SOLO study, re-ran the NEAT comparison but this time involved fos-amprenavir which was boosted by the addition of ritonavir⁸. Six hundred and sixty treatment naïve individuals were randomised to receive open-label treatment with either fos-amprenavir/ritonavir (1400mg/200mg once daily) or nelfinavir (1250mg twice daily). Again, abacavir and 3TC formed the NRTI backbone.

Again, this study recruited an advanced population, the median viral load at entry being 4.8 log copies, and the median CD4 count around 170 cells. After 48 weeks, by ITT M=F analysis, similar proportions reached the below 400 and below 50 copy cut-offs (68% fos-amprenavir versus 65% nelfinavir, and 56% versus 52% respectively). Treatment discontinuation occurred in 25% of fos-amprenavir users and 15% of nelfinavir users, and so the on treatment analysis provides quite different results: 95% and 91% of those

glossary

see also pages 7 & 9

adherence The act of taking a treatment exactly as prescribed.

antiretroviral A substance that acts against retroviruses such as HIV.

baseline Starting point or value.

bilirubin A chemical released by the liver as a result of damage caused by infection or drugs. Levels are assessed in the diagnosis of liver problems.

blinded (see open-label)

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. Popularly associated with atherosclerosis.

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

cross-resistance The mechanism by which HIV that has developed resistance to one drug may also be resistant to other, similar drugs.

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

HDL cholesterol (High density lipoprotein) cholesterol High levels of this form of cholesterol protect against heart disease.

hypersensitivity An allergic reaction.

new protease inhibitors continued

remaining on randomised treatment at 48 weeks had viral load below 400 copies, and 78% and 72% were below 50 copies. The median CD4 increase was approximately 200 cells in each arm.

Those who experienced virological failure were entered into a sub-study which genotyped participants for drug resistance mutations. Whilst there were significant differences in the frequency with which these were observed, when these data were presented in Glasgow in late November, they were challenged by Joep Lange, President-Elect of the International AIDS Society. Primary or secondary protease mutations were observed in 0 of 32 evaluable fos-amprenavir recipients and 30 of 54 nelfinavir recipients. In comparison, NRTI resistance was seen in 3 of 32 and in 31 of 54 respectively. When 3TC-containing, PI-based HAART regimens fail to suppress viral load, the typical pattern is for 3TC resistance to be observed rather than PI resistance. As Lange noted, the near absence of 3TC mutations amongst fos-amprenavir users here suggests these individuals may not have been taking their treatment at all.

Mild to severe side-effects were similar between arms, excepting an excess of diarrhoea in the nelfinavir group. There was a significant difference in the frequency of moderate to severe (Grade 3 or 4) increases in triglycerides: occurring in 6% of fos-amprenavir users and 2% of those taking nelfinavir. Abnormalities in levels of total or LDL cholesterol were seen less commonly, in less than 1% of participants.

Comment

So what do NEAT and SOLO really tell us about fos-amprenavir? Well, though one cannot condone the making of cross-study comparisons, it is tempting to look at these results and wonder about the risk:benefit ratio of adding ritonavir rather than taking fos-amprenavir as a

sole PI. SOLO seems to have found little extra efficacy, but worse tolerability, particularly regarding metabolic values. The boosting effect shifts the regimen from twice daily to once daily, and though this will no doubt be claimed as a victory for adherence watchers everywhere, the real change is from two capsules twice a day to four capsules once a day, and there is no evidence that dosing variations of this type have a significant impact on adherence, though some people may prefer a once daily regimen.

It's possible that the real attraction of ritonavir-boosted fos-amprenavir will be for treatment experienced patients, because over-coming drug resistance is a function of the relationship between drug exposure and viral replication – and boosted PIs tend to produce better exposure. At present this amounts to conjecture, however, as there are no data on the effects of this combination in PI-treated individuals.

Resistance and interactions

Because fos-amprenavir converts to amprenavir in the body, resistance to fos-amprenavir is likely to involve a similar pattern of mutations. This may prove to be a strength of this new therapy as amprenavir is generally considered less cross-resistant than several other PIs. As noted, boosting with ritonavir may change the frequency of clinical resistance to the drug however, so this will be worth looking out for in future.

Whilst efavirenz reduces fos-amprenavir levels, the addition of ritonavir brings these back in to a more normal range.

Access to fos-amprenavir

Fos-amprenavir is available in the UK via a named patient programme for anyone who, in the opinion of their doctor, would benefit from taking a PI with a low pill burden. Details of the scheme are available at aidsmap.com. GSK are able to field enquiries from doctors in relation to this programme but not from patients.

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adherence: elements of success

UK takes the lead in establishing clinical guidance on supporting HIV treatment adherence by *anna poppa*

Late last year, recommendations from the British HIV Association (BHIVA) and the Medical Society for the Study of Venereal Diseases (MSSVD), on how adherence to anti-HIV therapies should be promoted within treatment centres prescribing HAART in the UK, were published in draft form on NAM's website aidsmap.com¹. This comprehensive document, amongst the first of its kind world-wide, sought to raise the profile of HAART adherence amongst those purchasing and providing HIV care in the UK.

As we reported in last month's *ATU*, HIV health care commissioning has been restructured this year, resulting in a more pressing need for evidence-based instructions of this kind. However, the central role of adherence in enabling successful use of HAART has been well-established for some time, and in this sense, the UK Adherence Guidelines can be viewed as an attempt to ensure the full potential of HIV treatment is realised both by individuals being treated, and by health care systems, which have an obvious interest in making certain that resources are not wasted.

In a field where the standard of care changes rapidly, and innovation is often driven by developments in biotechnology, the basics may sometimes be over-looked. As the World Health Organisation state in a 2001 report on adherence to chronic therapy, "Increasing the effectiveness of adherence interventions may have far greater impact on the health of the population than any improvement in specific medical treatments."²

Adherence & HIV prognosis

Though highly effective in treating the ill effects of HIV infection, antiretroviral therapy requires patients to maintain an unusually high level of adherence if they are to sustain benefit. Though

adherence levels around the 50% mark are the norm in general medicine, HAART requires far greater levels.

In a frequently cited paper, Paterson and colleagues demonstrated that people whose adherence to protease inhibitor (PI)-based HAART regimens was below 95% were much less likely to gain virological or immunological benefit than those with adherence levels above 95%. Lower adherence was also associated with more days in hospital³. Whilst median follow-up in this study was just six months, data from a much larger Canadian cohort found that high levels of adherence reduced the risk of death by 17%⁴. In addition, improvements in adherence to HIV treatment have been shown to yield substantial clinical benefits. In a San Francisco study involving homeless people, each 10% increase in adherence resulted in a 21% reduction in disease progression⁵.

Which interventions work?

Despite the vast waste of health care resources which is incurred through low adherence, the medical literature evaluating the effects of adherence interventions is sparse. Brian Haynes of McMaster University, Ontario, and an expert in this area, has conducted several systematic reviews of randomised controlled trials which have assessed the impact of adherence interventions on adherence and disease outcomes. The latest in this series was published in a recent issue of the *Journal of the American Medical Association*.⁶

In a journal search which elicited just 33 studies considered to be methodologically sound, Haynes and colleagues found that only half of these reported improvements in medication adherence. Improved treatment outcomes were observed even less frequently; in just seventeen of 39 interventions. Whilst adherence to treatment

glossary continued
intent-to-treat analysis A form of statistical analysis of clinical trials, where data from all participants enrolled in the trial is evaluated, rather than data only from those who complete the trial.

LDL cholesterol (Low density lipoprotein) cholesterol High levels of this form of cholesterol increase the risk of heart disease.

lipid A general term for fats.

median The central value of the distribution, so that half the values are less than or equal to it and half are greater than or equal to it.

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

mutation A single change in gene sequence.

NNRTI Non nucleoside reverse transcriptase inhibitor, the family of antiretrovirals which includes efavirenz, nevirapine and delavirdine.

NRTI Nucleoside analogue reverse transcriptase inhibitor, the family of antiretrovirals which includes AZT, ddI, 3TC, d4T, ddC and abacavir.

on treatment analysis Method of analysing clinical trial results which includes only those participants who remained on their allocated study treatment.

courses of less than two weeks duration was found to be improved by relatively straight-forward measures such as patient counselling, information provision and memory aids, adherence to long-term (chronic) therapy required more complex, labour-intensive options.

Of the thirty chronic treatment trials which Haynes and colleagues reviewed, two concerned use of HAART. These two papers, both from Spanish research groups, are amongst the remarkably few HIV treatment trials which have investigated the effects of adherence interventions in a randomised fashion, and have been published. As such, they represent the best evidence we have for good practice models in this area.

Tuldra and colleagues compared a multi-faceted 'psychoeducative' intervention with standard follow-up in patients beginning a new HAART regimen⁷. The intervention was designed to increase self-efficacy around taking medication, and involved explaining the rationale for taking HAART and the role of adherence in preventing resistance; 'solving doubts' about medication intake; involving the patient in designing a medication schedule, and in development of strategies to manage problems relating to forgetting or delaying doses, side-effects, and changes in daily routine. Telephone support was available between clinic visits. During follow-up visits, the need for high adherence was reinforced, and problems were reviewed and coping strategies proposed. Strategies most commonly involved modification of dosing schedules, encouragement of habits to spur medication intake, and supporting patients to manage side-effects. Improved adherence levels (the proportion taking more than 95% of prescribed doses), and treatment responses (the proportion with viral load below 400 copies) were observed in the intervention group after 48

weeks follow-up. There were no differences between the two arms until this point however, suggesting that long-term adherence support is required to enable long-term effectiveness. Initial adherence levels in both arms were relatively high, but fell off in the control arm by 48 weeks, suggesting initial success may not be maintained without ongoing support.

Knobel and colleagues randomised 170 people (2:1) taking AZT/3TC/indinavir to receive standard care, or to receive detailed information on their therapy and for it to be adapted to their lifestyle⁸. Adherence was measured by structured interview and pill counts. Patients who took more than 90% of their doses were defined as adherent. After 24 weeks, there was a significant difference in adherence between groups (76.7% intervention versus 52.7% control), but no difference in proportions with viral load below 50 copies.

Getting long-term support

Tuldra and colleagues are not alone in concluding that people taking HIV therapy require ongoing support around their medication adherence if treatment is to be effective long-term, (and indeed this is one of the key recommendations of the UK Adherence Guidelines). In April last year, a group from the US Community Programs for Clinical Research on AIDS (CPCRA) published an important paper on outcomes observed in people on HAART whose adherence was measured over a one year period⁹. 'Longitudinal' data of this kind are extremely rare in the HIV medical literature.

This study involved people taking part in two separate randomised CPCRA trials:

- The PIP study (CPCRA 057), which investigated the effects of salvage regimens in people who were PI-experienced.

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Table 1: Response to HAART according to level of adherence, adapted from Mannheimer 2002⁹.

Adherence level	100%	80-99%	0-79%
Change in viral load level at 12 months (logs)	-2.77	-2.33	-0.67
Patients with viral load below 50 copies at 12 months (%)	65.6	47.1	16.7
Increase in CD4 cell count at 12 months	178.9	159.4	53.0

Table 2: Response to HAART according to consistency of adherence, adapted from Mannheimer 2002⁹.

Number of clinic visits where 100% adherence was reported	4	3	2	1	0
Patients with viral load below 50 copies at 12 months (%)	72	66	41	35	13
Increase in CD4 cell count at 12 months	178	188	145	106	92

- The FIRST study (CPCRA 058); a trial for people beginning HAART for the first time. Regimens were either PI-based, NNRTI-based, or contained both a PI and an NNRTI.

In total, 1095 people reported their adherence to their HIV therapy using a validated self-complete questionnaire, filled in one month and four months after starting treatment, and every four months thereafter. Those who reported 100% adherence were more likely to have an undetectable viral load after a year on treatment; experienced a significantly larger drop in viral load; and gained significantly more CD4 cells, compared with those reporting adherence levels of 80-99%, or of 0-79% (see table 1). This demonstrates clearly the difference which just a few missed doses could make.

The consistency of adherence over time was also a key predictor of longer-term success. As table 2 shows, the best results were seen in those people who reported taking all of their pills all of the time. In contrast, reporting 100% adherence at some but not all clinic visits was associated with a poorer response to treatment. Clearly this finding has great significance not only for people taking treatment, but for those providing clinical services; one-off interventions which coincide with starting a new HAART regimen may fail to produce long-term benefit if ongoing support is lacking.

Adherence & regimen factors

As we report in this month's accompanying article, recent years have seen a gradual move away from PI-based HAART regimens, in part due to concerns about toxicity, but also because many of the older PI regimens are often considered too difficult for many patients to manage. In comparison, NNRTI-based regimens, and those containing three NRTIs are generally dosed once or twice a day, have lower pill burdens, and fewer dietary restrictions; all

factors which can enable better adherence. Newer PIs, and boosted PI regimens which remove these class-based distinctions are now available, however.

The longitudinal study quoted above did report a greater frequency of 100% adherence at months 4 and 8 of follow-up in those receiving NNRTIs compared with PIs. Whilst frequency of dosing was not reported in this study, recommended PI regimens in the FIRST study contained either indinavir (dosed three times daily when taken as a sole PI), nelfinavir (which was still dosed three times daily when this trial began), or two PIs selected by the patient and doctor. NNRTIs were dosed once or twice daily. Pill burden was not found to affect adherence, suggesting that other regimen-related factors may have been at work.

Future research

If we need more information about how to support those taking HIV therapy, where will it come from? In the US, two studies are currently recruiting participants. The first, from the CPCRA, randomises naïve and treatment-experienced patients, who are starting a new HAART regimen, to receive an electronic medication reminder, assignment to a member of staff who acts as their Medication Manager, both of these interventions, or usual care.

The second trial investigates the role of direct observation by a health care worker in assisting adherence, a strategy employed in many settings where TB treatment is taken. Participants beginning HAART for the first time will be randomised to standard care or to observed therapy (where one dose is observed five times per week) for 24 weeks. Observed therapy patients will switch to standard care at this point. Details of these trials can be found at a new US-focussed patient information website <http://aidsinfo.nih.gov/>.

glossary continued
open-label A clinical trial where both the researcher and participants know who is taking the experimental treatment.

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

protease inhibitor
Family of antiretrovirals which target the protease enzyme. Includes amprenavir, indinavir, lopinavir, ritonavir, saquinavir, nelfinavir.

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.

wild-type Virus that has not been exposed to anti-HIV drugs before.

UK anonymous HIV surveillance: Update

Following on from our report on HIV in the UK in last month's *ATU*, the Communicable Disease Surveillance Centre (CDSC) released the latest findings from its anonymous HIV testing programme in December, to coincide with World AIDS Day. During 2001, the programme screened some 630,000 blood or saliva samples to assess prevalence of HIV, hepatitis B and hepatitis C in Britain.

According to the CDSC, one in twenty gay and bisexual men having a syphilis test in a London GUM clinic in 2001 were HIV-positive. Amongst those aged below 24, the HIV prevalence was 4%, indicating the extent of HIV transmission amongst this community in recent years. Many gay men remain unaware that they have HIV; 56% of those screened anonymously in this programme, who could have been diagnosed if they had volunteered for testing, did not do so. Acute sexually transmitted infections were more common amongst men who were unaware of their HIV infection. Between 1997 and 2001, voluntary HIV testing amongst gay men increased from 40% to 54% in London, and from 60% to 64% outside London.

HIV infection was found in one in 21 heterosexual men and one in 13 heterosexual women born in sub-Saharan Africa who attended a GUM clinic in London in 2000/01. Amongst UK-born heterosexual attendees prevalence was much lower (one in 428 men and one in 573 women).

Though the prevalence of HIV infection amongst injecting drug users remains relatively

low in the UK at around 1%, members of this community face high rates of hepatitis B and C infection (21% and 35% respectively).

Hepatitis C is a significant problem amongst those who started injecting within the previous three years, rising from a rate of 8.4% in 2000 to 17.0% in 2001.

Reference: CDR Weekly 28 November 2002, PHLS Communicable Disease Surveillance Centre. Further information from the Unlinked Anonymous Screening Programme can be viewed at http://www.phls.org.uk/topics_az/hiv_and_sti/hiv/epidemiology/ua.htm

Increase in needle sharing in the UK

Britons injecting drugs during the late 1990s were more likely to share needles to do so than in the earlier years of the decade. Prevalence of hepatitis B, a blood-borne virus easily transmitted through this route, rose in this group between 1997 and 2000, raising concern that drug injectors may face a growing risk of HIV and hepatitis C infection.

These findings, reported by the Communicable Disease Surveillance Centre in a recent issue of *AIDS*, were derived from an ongoing surveillance programme involving drug injectors using UK drug services. These services are in England and Wales, and so do not reflect drug use elsewhere. Twenty per cent of those participating in the programme were recruited in London.

The rate of needle sharing within the last month had fallen in the early 1990s, but between 1997 and 2000 rose from 27% to 41% in London, and from 17% to 29% elsewhere. These increases were seen in both men and women, and at all age groups.

The report's authors note that people injecting drugs may employ a range of strategies to reduce risk of infection, including cleaning needles before re-use, and sharing needles selectively. Much like unprotected sex, needle sharing may not always present a real risk of transmission of infections. Nonetheless, an increase in HIV incidence amongst injecting drug users in Vancouver has recently been reported, despite the availability of needle exchange facilities. This increase has been linked to a growth in the frequency of injecting.

Reference: Hope VD et al. *AIDS* 2002;16(18):2494-6.

Tenofovir kidney problem case report

Kidney failure and Fanconi Syndrome, a form of serious renal dysfunction, have been reported in a French woman taking the anti-HIV drug tenofovir (*Viread*). Published in the *American Journal of Kidney Disease*, this is the first case report of kidney failure linked to this anti-HIV drug.

Tenofovir is a nucleotide analogue, a type of NRTI. Research into the use of another drug from this class, adefovir, was abandoned because of weak anti-HIV potency and a tendency to produce kidney problems in people taking it. A third drug of this type, cidofovir, has also been associated with Fanconi syndrome and renal failure.

Though originally a worry during the early days of tenofovir's development, subsequent investigation has not so far identified kidney toxicity as a significant side-effect of this drug. Licensed in the European Union and the USA a year ago, tenofovir has been well-received by HIV doctors after a series of positive trial results suggesting its relatively good tolerability. It's price has been less popular – it's the most expensive of current antiretrovirals by some way.

A 45 year old woman with HIV and hepatitis C coinfection began anti-HIV treatment in 1995. After taking a series of antiretrovirals, tenofovir was begun in June 2001, alongside several other medications. Relevant laboratory tests at the time (including serum creatinine, a marker of kidney function) were normal, but five months later the woman was admitted to hospital and diagnosed with renal failure and Fanconi syndrome. On stopping tenofovir, her kidney function improved. Four weeks later, her serum creatinine level normalised.

Though this is an isolated case report of this problem, the authors advocate that people taking tenofovir may require ongoing monitoring of creatinine and electrolytes.

Reference: Verhelst D et al. *Am J Kidney Dis* 2002;40:1331-33.

Gates sponsors tenofovir HIV prevention study

An international trial investigating the effectiveness of a single anti-HIV drug in preventing sexual transmission of HIV is to begin following the announcement that the Bill and Melinda Gates Foundation, which represents the philanthropic activities of Microsoft's founder and the world's richest man, is to fund the study to the tune of \$6.5 million. The drug to be assessed is tenofovir, a licensed HIV treatment.

Interest in this potential application of tenofovir has been building since its early development, when experiments conducted in monkeys found the drug protected the animals from SIV infection, the simian form of HIV. The drug remains in the body for long periods after dosing and is taken just once a day. It's highly potent against HIV and is considered to have a good toxicity profile, though it has been in use for a relatively short period and, as the report above suggests, may occasionally produce significant problems.

The trial will be run in resource-poor countries and will recruit participants who are sexually active and at ongoing risk of HIV infection. Antiretroviral therapy has been found effective in reducing HIV transmission from mother-to-child and via occupational exposure. This is the first structured attempt to employ an antiretroviral pre-exposure prophylaxis strategy against sexual transmission.

New efavirenz formulation available

A single tablet version of the NNRTI efavirenz (*Sustiva*) is now available in the UK. This formulation can be used in place of the previous three capsule regimen. Bristol-Myers Squibb, efavirenz manufacturers, are offering the single tablet at the same price as the three capsules.

atu survey

Thanks to everyone who's returned their 2002 ATU Readers Survey. By the time you receive this issue we should be well on the way to analysing your responses and planning the changes you've asked for.

nam forum dates 2003

NAM Patient Information Forums will take place on these dates in 2003. The venue remains the University of London Union, Malet Street, W1, and topics will be announced in ATU and on aidsmap.com.

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February 24th
March 31st
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May 19th
June 30th
July 28th
September 29th
October 27th
November 24th



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For more information, and details of our other publications and services, please contact us, or visit our website, www.aidsmap.com.

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