

aids treatment update

New HIV treatments

It's been quite a lively summer for HIV treatments. New drug approvals, plus the early closure of under-performing treatment arms in a series of clinical trials, have provided the HIV community with plenty to talk about.

Amongst the many issues raised by the studies in question is the somewhat unresolved problem of how best to start therapy in people with high viral load, people we know are often more vulnerable to early treatment failure. In a country which has now licensed nineteen drugs for the treatment of HIV, it seems a curious decision to have entered people with advanced disease into trials which would provide them with first-line regimens we already know to be 'un-preferred' in this patient group.

Our willingness in the HIV community to be seduced by the new is an impulse which repeatedly comes back to bite us. So while earlier examples of European drug licensing authorities taking longer than their American counterparts to approve new antiretrovirals has induced pique, the slower passage through the EU of the most recent batch of therapies seems not to have been challenged so strongly. HIV treatments with improved tolerability will always be desirable, but we don't seem to be short of agents for which we haven't settled on a best use.

future options 2

PI boosting 6

news in brief 10

future options

2 a cautionary tale about the HIV community and new HIV treatments by anna poppa

After a somewhat fallow period in the cultivation of new HIV therapies, the 2003 harvest is looking more bountiful. Following the launch of T-20 in Europe in early July, FTC is now expected to be licensed by November, and atazanavir in the New Year.

Of course, the maturing HIV community demands much more today from new HIV treatments than perhaps we have in the past, and accordingly the reception for these additional agents has been somewhat mixed. If we needed any more reminders of how we got to be so hard to please, a couple of recently issued warnings about new-ish antiretrovirals have offered a few clues. After making eyes at tenofovir at its initial launch less than two years ago, our love affair with that drug has waned – reports of infrequent, though potentially severe, side-effects continue to appear, and now news of unforeseen drug interactions have seemingly reduced the options for partnering tenofovir with other treatments. As we review the next generation of HIV therapies, will we ever learn to manage our expectations better?

Warning on tenofovir/3TC/abacavir

At the end of July, the European Medicines Evaluation Agency (EMA), who are responsible for licensing drugs within the European Union, issued a public statement warning against the combined use of tenofovir, 3TC and abacavir for treatment of HIV.¹ This followed observations of poor performance when these drugs were given as a once-daily regimen in two separate trials. The cause of these results is not known at this time.

Tenofovir, 3TC and abacavir belong to the NRTI class of HIV treatments. Tenofovir is manufactured by Gilead and is licensed for once-daily use. 3TC and abacavir are made by GlaxoSmithKline (GSK), and though both were

originally licensed as twice-daily regimens, 3TC's indication was later expanded to include once-daily use. Abacavir's potential as a once-daily therapy has been under investigation, but it is not licensed for this purpose.

ESS30009 is a GSK-sponsored study comparing the NNRTI efavirenz with tenofovir, each taken alongside 3TC and abacavir, in people new to HIV therapy. The study was designed to evaluate GSK's new formulation of 3TC and abacavir which provides both drugs in one fixed-dose combination tablet, which is taken once a day. In a letter to health care professionals, the company reported that early viral load responses in recipients of tenofovir/3TC/abacavir were very poor relative to those seen in the efavirenz arm. Consequently, GSK closed the tenofovir arm early and reported their observations to the EMA and other similar authorities, and via a 'Dear Doctor' letter to healthcare providers.²

In this randomised, open-label study, early virological non-response was defined as either:

- a failure to achieve a two log drop in viral load from baseline by week 8, or
- a one log increase above the nadir (lowest ever) viral load on any subsequent visit.

By the eighth week of allocated treatment, 49% of the tenofovir arm (50 of 102 people) met one of these criteria, compared to 5% (5 of 92 people) in the efavirenz arm. In those participants who had been followed for a further four weeks, the failure rates were similar; 48% (30 of 63) of the tenofovir arm and 5% of the efavirenz arm (3 of 62) were virological non-responders by week twelve.

Baseline characteristics of those entering the trial have not been released publicly. In fact the only additional information reported by GSK concerned 'preliminary' resistance test results performed on fourteen people from the tenofovir arm who experienced viral load failure. It is not known how these fourteen were selected, and what is meant by 'preliminary' genotyping, so there is a danger in over-interpreting this information. For the sake of sharing, however, all fourteen were reported to be harbouring a resistance mutation (M184V) which is classically associated with 3TC, but which can also emerge during abacavir therapy. Eight of the fourteen were also found to be carrying the K65R mutation. This mutation is selected by both abacavir and tenofovir.

A second trial – same problems

A second trial investigating the use of a once-daily regimen of tenofovir/3TC/abacavir was reported at a recent International AIDS Society (IAS) conference in Paris.³ The rationale for this pilot study, carried out by the AIDS Healthcare Foundation, Los Angeles, was that this regimen would be easily tolerated. By avoiding the common NRTI alternatives d4T and AZT, the investigators were hoping to avoid side-effects associated with these therapies – particularly fat loss (lipoatrophy).

Nineteen people were recruited, all of whom were new to HIV treatment. On entering the study, the average viral load was 150,000 copies, and just under half the group had a viral load over 100,000 copies. The average CD4 count was 273 cells. Participants were considered to be non-responders if their viral load had not fallen by at least two logs within eight weeks, or had rebounded after having been suppressed.

After eight weeks, eleven people had experienced virological failure (nine of whom rebounded), two adherence-driven failure, and one toxicity-driven failure. This left just five participants who could be classed as responders; 27% of the group. Once again, resistance data are difficult to interpret – only two of those whose treatment failed virologically were found to have wild-type virus at that time. However, baseline resistance testing had found wild-type virus in just six participants.

What do these results mean?

Both the EMEA and GSK have issued strong warnings against the use of this particular triple NRTI combination, while these initial reports are examined further. Investigators with the AIDS Healthcare Foundation read the data a little differently, urging caution specifically around the once-daily use of these drugs, which is, after all, the regimen which has been under scrutiny.

There is no evidence of a negative interaction between tenofovir and 3TC; in fact one of the pivotal studies leading to tenofovir's approval reported very positive results over 96 weeks using tenofovir/3TC/efavirenz in people new to treatment.

Abacavir and 3TC have clearly been widely used together, though largely in their original twice-daily dosing regimens. That leaves an interaction between abacavir and tenofovir looking like a possible culprit, though the contribution of the switch to once-daily dosing of abacavir and 3TC also needs unpicking. If interactions have conspired to produce inadequate drug exposure, it's perhaps to be expected that this regimen might then be particularly vulnerable to the emergence of resistance, given the overlaps in mutational patterns which the three agents select.

Sadly, it looks like a considerable number of participants in these trials have come off rather badly, experiencing rapid regimen failure which in many cases has left behind significant resistance mutations. What are the lessons to be learnt?

Firstly, it's unclear how much pharmacokinetic exploration of the regimen was performed prior to recruiting participants to either study, but it doesn't seem to have been enough. Secondly, there may need to be a reassessment of the supposed need for all antiretrovirals to be dosed once daily, regardless of how well this suits them pharmacologically. There is a distinct whiff of the tyrannical around once-daily HIV therapy – one size does not fit all.

New data on atazanavir

As we've previously reported, the experimental protease inhibitor (PI) atazanavir appears not to induce the blood fat (lipid) abnormalities which accompany the use of other PIs (see *ATU* issue 121), and further encouraging data on this issue were presented in Paris. Study

glossary

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.

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. High levels can be associated with atherosclerosis.

CT scan Computed tomography scan, a medical monitoring technique which turns a series of X-rays into a 2-dimensional, cross-sectional image. *continued on page seven*

references

1. EMEA, London, 30 July 2003. <http://www.emea.eu.int>
2. GlaxoSmithKline July 2003.
3. Farthing C. 2nd IAS Conference on HIV Pathogenesis and Treatment (IAS Conference), Paris, abstract 43, 2003.
4. Jemsek JG. 2nd IAS Conference, abstract LB13, 2003.
5. Bristol-Myers Squibb.
6. Sanne I. 14th International AIDS Conference, Barcelona, abstract TuPeB4433, 2003.
7. Raffi F. 2nd IAS Conference, abstract 38, 2003.
8. Molina JM. 2nd IAS Conference, abstract 37, 2003.

future options continued

BMS-034 compared atazanavir with efavirenz, alongside AZT/3TC, in people new to treatment. An earlier presentation from this study reported similar virological and immunological response to treatment between the two arms over 48 weeks. Atazanavir treatment resulted in either no change or an improvement in lipid levels, and whilst efavirenz tended to raise some metabolic parameters, the level of increase did not merit intervention.

Two hundred and eleven 034 volunteers (around a quarter of the full study population) entered a metabolic sub-study in which DEXA and CT scans performed at baseline and at 48 weeks were used to monitor body shape changes.⁴ Both atazanavir and efavirenz were associated with body fat gain during the study period, but in a pattern typical of weight gain rather than lipodystrophy. There were no differences observed between the two treatments.

A further analysis from the 034 study appears likely to resolve some of the concerns about potency which arose when viral load results from this trial were first presented. Though there was no difference between arms in the likelihood of viral load falling below 50 copies, the proportions which did so were surprisingly low (32% and 37% at 48 weeks by intent to treat analysis). BMS have now presented new information suggesting that the test tubes used to transport samples from trial volunteers were at fault, producing falsely high viral loads in both treatment arms.⁵

Perhaps the key question which still hovers over atazanavir is whether it should be used as a single PI in any circumstance, rather than being boosted with ritonavir. This subject is covered in this month's accompanying article.

Positive opinion on FTC

FTC (emtricitabine, *Emtriva*) is a new NRTI marketed by Gilead which was approved in the US at the beginning of July. The EU's Committee

on Proprietary Medicinal Products (CPMP) issued a positive opinion on the drug's licensing within member states, which gives the go-ahead to full marketing authorisation being granted in Europe by the beginning of November.

FTC is a 3TC-like compound (meaning their chemical structures are very similar) which is given as a once-daily single capsule containing a 200mg dose, and can be taken with or without food. Its activity against HIV and its side-effect profile are also comparable to those of 3TC. Both drugs are active against hepatitis B virus, as well as against HIV, though FTC is not licensed for this purpose. And just like the GSK drug, FTC selects the M184V mutation, and this confers high level resistance to both drugs. This means that virological failure on one is likely to rule out successful use of the other, though there is some evidence to suggest that viral load failure on FTC leads to M184V emergence less frequently than does viral load failure on 3TC.⁶

Aside from this last point, there is little to distinguish the two drugs clinically. 3TC is commonly used as part of the fixed dose formulation *Combivir*, which also contains AZT and provides both drugs in a single tablet taken twice daily. If Gilead can successfully advance their plans to launch a fixed dose combination of FTC and tenofovir, a once-daily slated to arrive by 2005, *Combivir* may have a strong rival. Gilead recently announced they had begun enrolling treatment naïve participants into a large Phase III international study comparing tenofovir/FTC with *Combivir*, each taken with efavirenz. This study will recruit 300 participants at sites in the US and Europe.

FTC versus d4T

One of two critical trials which has enabled FTC's approval, the FTC-301 study set the drug against d4T in 571 people new to HIV therapy, all of whom also received once daily ddI and

efavirenz. Treatment allocation was blinded by placebo, and so all participants received a twice-daily regimen. Ordinarily, of course, the FTC regimen would be taken once daily.

Final results from the study were presented at the IAS meeting in Paris.⁷ At entry, average viral load was 4.8 log, with 40% of participants having a viral load above 100,000 copies. Average CD4 count was 318 cells.

A planned interim analysis led to the study being unblinded, as it was noted that one arm was clearly outperforming the other. At 48 weeks, more people allocated d4T had left the trial early than those randomised to FTC. Regarding causes of discontinuation, however, the only significant differences were in the proportions stopping because of side-effects (5.6% on FTC versus 11.6% on d4T), and for treatment failure (2.8% versus 7.7% respectively).

After 60 weeks, by intention to treat analysis, FTC recipients were more likely to have a viral load below 400 copies than those receiving 3TC (79% versus 63%); and also more likely to be suppressed below 50 copies (75% versus 54%). The risk of treatment failure due to side-effects was calculated to be 7.4% for FTC, and 16.6% for d4T at this time-point. The 60 week probability of viral load failure was also lower with FTC (6.0% versus 14.5%).

All in all, these results demonstrate the superiority of the FTC-containing regimen in treatment-naïve people, though it's worth restating that, as is often the case, the comparator arm in this study is one which is no longer standard of care. The combined use of d4T and ddI has been shown to be poorly tolerated.

Switching to FTC

The once daily combination of FTC/ddI/efavirenz was under investigation as a maintenance regimen in the French ALIZE study (ANRS 99).⁸ This open-label study randomised 355 people who were virologically controlled on a PI-based regimen to either remain on their PI therapy, or switch to the once daily FTC combination.

Participants were NNRTI-naïve and were mainly taking either indinavir or nelfinavir at entry, neither as boosted PIs, and the average time for

which viral load had been suppressed under PI-HAART was 35 months. The most common NRTI backbones at entry were AZT/3TC and d4T/3TC. Forty-six per cent of the group had received NRTIs alone before their PI.

One year after the switch, 36 people had stopped allocated treatment, and these were equally distributed between the two arms. There was no difference amongst the remaining participants in the proportions with viral load below 400 copies at this point (93% versus 95%).

One of the aims of this treatment strategy is to improve abnormal lipid levels which can occur as a side-effect of PI-based HAART. Existing data suggest that switching to efavirenz may not be the most reliable way of achieving this goal, compared to a switch to either nevirapine or abacavir. Amongst ALIZE participants, there were no differences in the effect of treatment on lipids over the 48 weeks, aside from a greater likelihood of gaining an increase in levels of the cardio-protective HDL cholesterol.

These data suggest that switching from stable PI-based HAART to an FTC-containing regimen results in continued virological control, and may improve some metabolic parameters.

key conclusions

- HIV doctors and patients have been warned against the combined use of tenofovir/abacavir/3TC after two trials found the combination failed to reduce viral load effectively. These results are unexplained at present.
- A trial looking for signs of body fat changes (lipodystrophy) in people taking either an unlicensed protease inhibitor, atazanavir, or efavirenz, has reported that this side-effect was not seen during the first year of treatment.
- A new HIV drug from the NRTI class, FTC, has passed the first stage of approval in the European Union, and should be available on prescription by November.

US atazanavir approval

In late June the US Food and Drug Administration licensed atazanavir for treatment of HIV. Branded *Reyataz*, and manufactured by Bristol-Myers Squibb, atazanavir is the first approved once-daily PI. European approval is not expected before early 2004. Until then, atazanavir is available via an expanded access programme and through participation in clinical trials (see aidsmap.com).

atazanavir plus tenofovir

Bristol-Myers Squibb have informed healthcare professionals that care should be taken when administering their PI atazanavir with the NRTI tenofovir. An interaction between the two reduces atazanavir exposure and increases tenofovir exposure. The clinical implications are not fully understood, but BMS suggest that ritonavir-boosting should overcome any risk of inadequate potency when atazanavir is used with tenofovir.

further reading

See aidsmap.com for a more detailed review of atazanavir and FTC. Position papers on these drugs are also available from the US Treatment Action Group at <http://www.aidsinfonyc.org/tag/index.html>

PI boosting

6 is it more art than science? by edwin j bernard

Since the early days of HAART, boosting a protease inhibitor (PI) with a small additional dose of ritonavir has been explored as a means of improving the effectiveness of drugs in this class. The first fixed-dose boosted PI, *Kaletra* (lopinavir/ritonavir) was approved in the US in September 2000 and in the European Union in April 2001.

As more data have shown a trend towards the superiority of boosted PIs over unboosted PIs, boosting has become increasingly mainstream. So much so, in fact, that the latest treatment guidelines from the UK¹ and the US² both suggest the use of a boosted PI (notably *Kaletra* and saquinavir/ritonavir in the UK, and *Kaletra* in the US), not only for second-line and salvage therapy, but also as a viable option for an initial regimen. As the BHIVA guidelines note, there's a lack of rigorous evidence regarding which strategy is best. Although the latest data presented at the 2nd International AIDS Society (IAS) Conference on HIV Pathogenesis and Treatment held in Paris last month do not answer that particular conundrum, there is new evidence to show that when it comes to efficacy not all boosted PIs are equal, and that boosting is not always better.

Why boost?

The way the human body metabolises drugs has evolved as a result of encountering toxic

substances in nature in an effort to survive. PIs, like many other substances we ingest, are known as xenobiotics; foreign substances that our bodies recognise and then attempt to detoxify, treating them as if they were dangerous. One of the ways that the body removes PIs is through a liver enzyme known as cytochrome (CY) P450 3A4. Ritonavir is a very potent inhibitor of this enzyme, which means that small doses of ritonavir lead to increased blood levels (hence the term 'boosting') of all currently approved PIs, with the exception of nelfinavir.³

This interaction between ritonavir and the other PIs has several very attractive benefits. It can simplify the regimen by reducing the pill burden, removing the need for food restrictions in the case of indinavir, and provide once-, or at most, twice-daily dosing. Just as significantly, since it raises the trough levels (the lowest blood level reached after dosing, known as C_{min}) of the boosted drug, ritonavir boosting is often able to overcome low levels of drug resistant virus – these might prevent the drug working if it were to fall to the lower trough levels which occur without boosting.

There is, however, a high degree of variability of boosted drug levels among individuals. Both the UK and US guidelines therefore recommend therapeutic drug monitoring (TDM), since ritonavir can also increase peak levels (known

as Cmax), which may lead to more short-term toxicities. Additionally, by increasing exposure to the boosted PI for longer periods of time (known as area under the curve or AUC) the risk of medium- and long-term side-effects, such as lipodystrophy and metabolic abnormalities that may lead to heart disease and diabetes, could also be increased.

Boosted saquinavir vs *Kaletra*

Boosted saquinavir was the first boosted PI regimen used and is one of the most studied. However, this was not a good conference for saquinavir/ritonavir. Last year, the MaxCMin1 study, which compared saquinavir gel caps (*Fortovase*)/ritonavir (1000/100 mg twice daily) to indinavir/ritonavir (800/100 mg twice daily) came out slightly in favour of saquinavir. In the intent-to-treat analysis saquinavir/ritonavir did much better than indinavir/ritonavir due to more people switching off indinavir/ritonavir for poor tolerability. The on-treatment analysis indicated that those able to tolerate their therapy achieved similar viral load declines and CD4 count increases.⁴

The results of MaxCMin2 study, a major head-to-head randomised comparison of the two rival boosted regimens *Kaletra* and saquinavir/ritonavir over 48 weeks, have been long-awaited. However, possibly because the trial was sponsored by Roche, manufacturers of saquinavir, the results reported in Paris were somewhat sketchy.

Nevertheless, it does appear that boosted lopinavir is superior to boosted saquinavir. Significantly, 30% of 161 people starting on saquinavir/ritonavir experienced treatment failure compared with only 20% of 163 starting on *Kaletra*, although most of the difference was due to discontinuations in the saquinavir arm due to adverse effects or "personal choice"; three discontinuations were due to virologic failure.

The real problem with interpreting the results presented here was that the trial encompassed both treatment-naïve and treatment-experienced patients (33% were antiretroviral-naïve, 48% were PI-naïve, and 32% had experienced virologic failure of at least one PI), and provided incomplete analysis of the three

separate populations, and no comparison of lipid and metabolic changes.⁵

More on *Kaletra*

According to manufacturers Abbott, *Kaletra* is currently the most widely-prescribed PI in both Europe (with a 30% market share) and the US (with a 28% market share).⁶ An Abbott-sponsored study presented in Paris provided a four-year follow-up of 100 people who began treatment with a combination of *Kaletra* plus d4T/3TC. Over an extended follow-up period of 216 weeks, 28 people stopped therapy. Analysing the data to include these people, viral load was below 50 copies in 70% of the group after four years. When they were excluded, the figure rose to 97%. CD4 cell count rose by 500 cells on average during the study period.⁷

Somewhat curiously *en vogue* in Paris, an NRTI-sparing pilot study from France (the BIKS study) presented 24-week data from an uncontrolled open-label 48-week trial using twice-daily *Kaletra* (533/133 mg) plus once daily efavirenz (600 mg). Participants had to have more than 100 CD4 cells and a viral load above 5000 copies, be NNRTI-naïve and, if PI-experienced, have less than five lopinavir-associated resistance mutations. Out of the 86 participants, only nine were PI-experienced, 21 had a prior history of antiretroviral therapy and the majority, 65, were antiretroviral-naïve.

After 24 weeks, 78% of all patients had a viral load below 400 copies with a median increase in CD4 count of 116 cells. Five patients experienced virologic failure. However, 14 patients (16%) left the study early, including three for central nervous system side-effects, three because of rash and one due to extremely high lipid levels. Indeed, there was a relatively high rate of adverse drug reactions seen overall, with almost 40% developing a grade 3 or 4 adverse event. Given that the driving force behind NRTI-sparing therapy is the avoidance of side-effects, these data are less than encouraging.⁸

A big boost for atazanavir

With the recent US approval of the new PI atazanavir, and its predicted licensing in the EU early next year, *Kaletra's* days in the limelight may be numbered, if preliminary results from

glossary contd

DEXA scan Dual Energy X-ray Absorptiometry, another scanning technique used to view cross-sectional images of the body.

enzyme A protein which speeds up a chemical reaction.

gene A DNA sequence which determines the structure of a protein.

genotype The genetic make-up of an organism.

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

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.

lipids A general term for fats.

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

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.

naïve Never having taken anti-HIV treatments before.

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

continued on page eleven

PI boosting continued

the 045 study (sponsored by atazanavir's manufacturers, Bristol-Myers Squibb) endure through longer follow-up. In this randomised study, 358 people who had experienced failure of at least two prior regimens, and of at least one agent from each of the three main drug classes, were randomised to either atazanavir/ritonavir (300/100 mg) once daily, or to atazanavir/saquinavir (400/1200 mg) once daily, or to *Kaletra* (400/100 mg) twice daily. These were taken with participants' existing NRTI backbone for two weeks, after which time this was switched to tenofovir and another new NRTI. All groups had an average of 2.5 years prior PI exposure, and five years NRTI exposure.

After 24 weeks, participants were just as likely to have a viral load below 400 or 50 copies on atazanavir/ritonavir (64% and 39%, respectively) as on *Kaletra* (62% and 42%, respectively). Boosted atazanavir did significantly better with regard to lipids: total cholesterol and triglycerides were reduced 8% and 2%, respectively, compared with increases of 3% and 41%, respectively, seen in patients on *Kaletra*. Seven atazanavir/ritonavir treated patients began protocol-mandated lipid-lowering therapy during the study, compared to fifteen *Kaletra* treated patients. Atazanavir is also dosed once daily, although studies are ongoing regarding once-daily dosing of *Kaletra*.

Although atazanavir boosts saquinavir in the test tube, only 44% and 23% of those on this combination achieved a viral load below 400 and 50 copies after 24 weeks, respectively. In this study, almost half of the cohort had less than four primary NRTI resistance mutations, which suggests that the addition of tenofovir and a new NRTI could have contributed a significant amount of antiretroviral potency. Since results were not presented prior to the two-week switch, the significance of the NRTI switch is not known. Additionally, approximately two-thirds of the

cohort had less than four primary protease resistance mutations. The acid test for boosted atazanavir in PI-experienced patients, however, is how it fares amongst those with more protease mutations, since, in test tube study at least, atazanavir trough levels are raised ten-fold when the drug is dosed with ritonavir.⁹

Unboosted atazanavir vs *Kaletra*

A second study reported in Paris provides less positive news on atazanavir's role in the HAART armamentarium. The BMS 043 study investigated a similar proposition to the 045 study noted above; the role of a new PI in people who have already experienced viral load failure on another PI. Study 043, however, tested *Kaletra* against unboosted atazanavir.¹⁰

Three hundred people with virological failure on their current PI-based regimen were randomised to one of the two new PIs, each taken in combination with two NRTIs. Median viral load at baseline was 4.16 copies, and median CD4 count was 275 cells. Participants had been on a PI for a median of 2.6 years, and just short of a quarter had at least four PI resistance mutations at baseline.

Over 24 weeks, viral load responses were significantly better in the *Kaletra* arm compared to those on unboosted atazanavir (77% versus 59% below 400 copies; 54% versus 38% below 50 copies, respectively). As we have come to expect, atazanavir was much easier on lipid parameters than *Kaletra*. But given the results of the 045 study, opinion continues to be divided on whether atazanavir should always be given boosted.

Double boosting

Utilising low dose ritonavir to boost both lopinavir and saquinavir, without other antiretrovirals, was the subject of two studies presented in Paris, one from the US in people who were naive to PIs, and one from Germany as a salvage regimen in the heavily PI-experienced.

The US double boosting data constituted the first 48 weeks of a 72-week open-label, uncontrolled, NRTI-sparing pilot study (sponsored by saquinavir manufacturers Roche), that combined saquinavir (*Fortovase* 1000 mg) and *Kaletra* (400/100 mg) twice daily in twenty PI-naïve patients with moderately advanced HIV disease (average CD4 was 274 cells and viral load 4.4 log copies). After 48 weeks, by intent-to-treat analysis, 70% of patients achieved viral loads of less than 400 copies, 65% reached 50 copies, and the average increase in CD4 counts was 194 cells.

Lipid increases were observed during follow-up. Two people were already taking lipid-lowering medicines on entering the study, and were joined by a further three during the 48 weeks. Four people left the study early (two because of side-effects), and six required an adjustment to their saquinavir dosage. Two remained in the study with the assistance of tenofovir intensification. Weight gain and site-specific fat accumulations were reported with some frequency, though the latter were subjectively measured, as the study protocol inexplicably did not allow for the use of DEXA or CT scanning. All in all, a less than persuasive exercise.¹¹

The German study looked at the same doses of saquinavir and *Kaletra* in 121 heavily pre-treated patients from the Frankfurt HIV Cohort who were experiencing treatment failure due to either resistance (58%), toxicity (39%) or both (3%). Twenty-four week results were available for 64, of whom 52 (81%) were still on therapy.

The focus of this presentation was to tease out the factors that led to a response to treatment, which was defined in one of four ways. If baseline viral load was below 400 copies then it should remain so at 24 weeks; if baseline viral load was between 400 and 1000 copies at baseline, it should remain below 1000 copies at 24 weeks; baseline viral load between 1000 and 100,000 copies should reach 5000 copies at 24 weeks; and if baseline viral load was above 100,000 copies, then a level of 10,000 copies or less should be achieved at week 24. Forty-five of the 52 were classed as responders. Responders were found to have a higher CD4 count at baseline (196 vs 66 CD4 cells) and had less PI resistance mutations at baseline (2 vs. 8). Although plasma concentration levels of both saquinavir and lopinavir were lower

in non-responders compared with responders, this did not reach statistical significance.

Unfortunately, there was no information on lipid levels or fat gain in this cohort.¹²

Long-term effects of ritonavir boosting

The latest research presented by pharmacologist Dr Charles Flexner in Paris showed that ritonavir also affects other enzyme systems that are important for drug transport and metabolism. These include CYP 2D6, GST gene, OATP, and MDR1 (the P-glycoprotein gene). This leads to the complex variety of drug-drug interactions associated with ritonavir, some of which can be life-threatening, as is the case with *Viagra*. However, little is still known about the long-term effects of modifying these enzyme systems. Since ritonavir also inhibits MDR1, this could allow not only more drugs, but also undesirable substances (like carcinogens) into the body and into cells. It may also counteract the blood-brain and maternal-fetal barriers that are set up to provide specific protection for these vital areas. Limited data so far suggest that ritonavir appears to have some anti-cancer effects that could possibly redress some of this imbalance.^{13, 14}

Since HIV itself is rather toxic and often immediately life-threatening, the science of boosting, as it is with all antiretroviral therapy, appears currently to be more of an art: balancing the benefits with the toxicities, both known and potential.

key conclusions

- Boosting single protease inhibitors (PIs) with a small amount of ritonavir can improve the effectiveness of the boosted drug.
- Boosted PIs are now recommended as a viable alternative to NNRTI-based combinations for those starting HIV treatment. They are also an option in people with resistance to other PIs.
- Like many HIV treatments, the longer-term effects of taking boosted PIs are not established at present.

future boosted PI options

Amprenavir and its pro-drug fos-amprenavir, along with tipranavir, are also candidates for ritonavir boosting. The latter two are experimental therapies, on which there were very few new data reported in Paris. More information on these treatments is available at aidsmap.com and in *ATU* issue 121.

references

1. Draft BHIVA Antiretroviral Treatment Guidelines, 2003 www.aidsmap.com/about/bhiva/bhivagd.asp
2. U.S. DHHS Guidelines, 2003 www.aidsinfo.nih.gov/guidelines/
3. Kempf. *Antimicrob Agents Chemother* 1997;41:654-60
4. Gerstoft. 42nd ICAAC, San Diego, abstract H-172, 2002
5. Youle. 2nd IAS Conference, Paris, abstract LB23, 2003
6. Abbott Labs Press Release 24/6/03
7. Kessler. *Antivir Ther* 2003;8(suppl 1):S338. Abstract 568.
8. Ferré. *Antivir Ther* 2003;8(suppl 1):S193. Abstract 36.
9. Badaro. *Antivir Ther* 2003;8(suppl 1):S212. Abstract 118.
10. Nieto-Cisneros. *Antivir Ther* 2003;8(suppl. 1):S212. Abstract 117.
11. Hellinger. *Antivir Ther* 2003;8(suppl 1):S339. Abstract 571A.
12. Staszewski. *Antivir Ther* 2003;8(suppl 1):S342. Abstract 583).
13. Gaedicke. *Cancer Research* 2002;62(23):6901-8
14. Pati. *Blood* 2002;99(10):2771-9

Heart disease in HIV

A recent review of HIV infected and uninfected people in California has reported a higher incidence of coronary heart disease in younger people with HIV compared to those without. The same study also noted an association between heart disease risk and exposure to HIV therapy, though only in adults aged below 33.

The analysis involved over 3 million recipients of Medicaid (a US state-administered programme which provides health insurance to people on low incomes), 28,513 of whom were HIV-positive. In men up to the age of 34, and in women up to the age of 44, proportionately more coronary heart disease events were seen in people with HIV than in the HIV-negative majority. Given this excess frequency, the authors conclude that heart disease prevention strategies should be targeted at younger people with HIV.

A second study from France supports this suggestion. Risk factors for heart disease (such as smoking, diabetes, high blood pressure, lipid values) were collected in 223 HIV-positive men taking a protease inhibitor, and compared with those in a similarly aged (35-44 years) group of uninfected men. Based on these data, the predicted risk of heart disease was forecast to be significantly higher in the infected men. A higher frequency of smoking meant that cigarettes contributed 65% of this risk in HIV-positive men.

Concerns about the future risk of heart disease should be balanced against the positive effects of HIV therapies in prolonging life and good health. This subject was last reviewed in *ATU* issue 123.

References: Currier JS. *JAIDS* 2003;33:506-12. Saves M. *CID* 2003;37:292-8.

KS relapse after switching off PIs

Doctors in France have reported a series of five people whose Kaposi's sarcoma (KS) re-appeared after they had switched their PI-based HAART for an NNRTI-based combination. The men's KS, a form of cancer which is diagnostic of AIDS, had been in remission for a median of 32 months whilst on PIs, but relapsed a median of 11 months after the switch.

The introduction of PIs was associated with a reduced incidence of many AIDS-related illnesses, including KS. Though much of this is considered to be due to the suppression of HIV and restoration of immune function which is induced by effective HAART, it has been suggested that PIs have an additional direct effect on cancers, which may not be shared by other HIV drug classes. This new evidence would appear to support this assertion, as all five individuals experienced a relapse of their KS despite a good immunological and virological response to their NNRTI-containing regimen.

Further data are needed to understand better the contributory role of therapy switches in this small case series. Nonetheless, the authors urge caution over switching away from PIs in people with a history of KS.

Reference: Bani-Sadr F. *AIDS* 2003;17(10):1580-1.

Drug resistance in untreated Europeans

Some 10% of people with HIV in Europe carry drug-resistant strains of the virus even before starting treatment, according to an international collaboration set up to monitor transmission of drug resistant HIV. Authors behind the CATCH study say these findings justify a stronger role for resistance testing in the selection of initial therapy.

CATCH was established to determine the prevalence of drug resistance in treatment-naïve Europeans during the period from 1996 to 2002. Data presented at a recent International AIDS Society conference in Paris involve 1,633 participants recruited from sixteen European countries and from Israel.

Using a genotypic testing method, primary resistance mutations were detected in 9.6% of the group. By drug class, mutations associated with resistance to NRTIs were seen in 6.9%; to NNRTIs in 2.6%; and to PIs in 2.2%. Genotypic resistance to two or more classes was noted in 1.7%.

Data gathered from France and the UK were not included in this analysis, though a separate report presented to an expert HIV resistance workshop earlier this year found a prevalence of 17% in treatment-naïve individuals in the UK from 2001 to 2003. Surveillance involved 1,968 untreated people recruited since 1996.

References: van der Vijver DAMC. 2nd International AIDS Society Conference, Abstract LB1, 2003. Pillay D. 12th International HIV Drug Resistance Workshop. Abstract 124, 2003.

Alternating regimens to treat HIV

A seemingly cumbersome approach to HIV therapy, whereby people alternate drug regimens rather than staying on the same one, has been shown to delay treatment failure in a pilot study led by Spanish doctors. The intriguing results of the SWATCH study were published in *Annals of Internal Medicine* in July.

SWATCH randomised 161 people to begin open-label HIV therapy with either d4T/ddI/efavirenz or AZT/3TC/nelfinavir, or to alternate between the two regimens, switching one for the other every three months without a break. The researchers hypothesised that switching regimens would shorten any period where failing treatments were continued, and thereby reduce the potential for drug resistance, and consequent treatment failure, to emerge.

Whatever the explanation, the approach proved effective over the short-term. After 48 weeks on treatment, those participants who alternated combinations were less likely to have experienced viral load failure than those on standard therapy. No other differences were detected regarding other parameters – CD4 changes, treatment adherence, side-effects and quality of life were all similar between arms. Given that many people will likely dismiss this strategy as running counter to the trend for 'simplification' of HIV therapy, these latter observations are important. Nevertheless, alternating regimens remains an experimental approach to HIV treatment which requires further study.

Reference: Martinez-Picado J. *Ann Intern Med* 2003;139:81-89.

Paris reports

This issue features new information presented at the 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment, held in Paris in July. Additional news stories from the conference were published at NAM's website aidsmap.com from July 14th.

A number of further online summaries are available. The Editor recommends the following:

- IAS <http://www.ias.se/pdf/632.pdf>
- Clinical Care Options for HIV <http://clinicaloptions.com/hiv/conf/ias2003.asp>
- The Body Pro <http://www.thebodypro.com/confs/ias2003/ias2003.shtml>

glossary contd

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

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

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

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.

salvage therapy Any treatment regimen used after a number of earlier regimens have failed.

toxicity The extent or ways in which a drug is poisonous to the body.

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

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

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