

AIDS TREATMENT UPDATE

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Less is more?

Durban International AIDS Conference changes focus of global research effort

BY ANNA POPPA

In the four years between the International AIDS Conference in Vancouver and the 13th Conference held in Durban last month, it has become clear that HIV eradication, the hot topic in Vancouver, is not an achievable goal with current drugs. Indeed, many of the same scientists who focussed on eradication back then are now engaged with the study of what happens when HAART is stopped and then re-started.

Interest in structured treatment interruptions (STIs) has grown at precisely the time that the 'HAART for life' strategy employed in the developed world has become less popular. For Tony Fauci, Director of the US National Institute of Allergy and Infectious Diseases (NIAID), this re-focussing isn't difficult to understand: "For most individuals, continuous HAART, although effective in many patients, can be toxic, difficult to adhere to, and, in many settings, prohibitive in cost".

At the same time as treatment access in poorer nations has become a focus of global HIV activism, many researchers are pursuing experimental HIV treatment strategies which *lessen* the role of HAART. Few of these are new – intervening later in the course of disease, using immune modulators as an adjunct or alternative to antiviral therapy, and taking breaks in treatment, have all been around the block a few times. But each of these strategies were the subject of key research presentations in Durban, where they seemed to have won favour through their relevance to people with HIV globally.

CYCLING TREATMENT

Fauci and colleagues at NIAID reported from an ongoing study of intermittent therapy at the Durban

conference¹. This enrolled patients whose viral load had been lowered below 50 copies for at least three months on HAART, and whose CD4 count was above 300 cells. Participants were randomised to either continue HAART, or to cycles of therapy consisting of eight weeks on treatment and four weeks off.

Findings presented in Durban were far from complete, which has roused a level of criticism. The study was designed to follow 70 people for 22 months, and yet viral load data were available for only nine intermittent HAART participants, who had completed two to three cycles.

All of these nine experienced the expected rebound in viral load off treatment, which was then suppressed back below 50 copies when HAART was re-started. It has been suggested from other STI studies that with each consecutive treatment interruption, viral load may rebound to progressively lower levels. This is proposed by some to be evidence that STIs induce a level of 'host control' of HIV, that is, better control of HIV by the immune system. In this NIAID study, no consistent pattern in rebounding viral load peak levels was observed, (if indeed it is meaningful to look for patterns in such a small patient group with such short follow-up). The data on

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this issue are not consistent – a Swiss-Spanish STI study presented in Durban found no evidence of a reduction in viral rebound with each successive treatment cycle².

Returning to the NIAID study group, CD4 counts fell with each cycle but returned to baseline on treatment. It's this last point which sets the alarm bells ringing for many of those who remain sceptical about the long-term value of treatment interruptions. Whilst the real cost of losing CD4 cells would appear relative to the number you have to lose, trusting that the tumble will be offset by other benefits, and can be reinstated by a further bout of HAART, is an act of faith for some, and runs contrary to accepted wisdom about the direction CD4 counts *should* be going in people taking treatment. As Brian Gazzard commented, reviewing Durban's clinical science presentations on the closing day, "I like to see the CD4 count in my patients going up, thank you very much".

CAUTIONS ON TREATMENT BREAKS

These new data from NIAID are preliminary and involve very small numbers of people followed for short periods. Whilst they are of interest, at the moment they prove nothing. Many of the claims which are made about STIs may turn out to be false. Viral load rebounds may simply re-seed those reservoirs of virus which exist beyond the blood, and which may have been depleted by HAART. But aside from the potential loss of the virological and immunological benefits accrued through taking HAART, there are other weaknesses in the STI hypothesis.

Firstly, as a Spanish group demonstrated in Durban, adherence may not be improved by taking breaks in treatment, but may mean the establishment of a pill-taking routine becomes even more of a challenge³. Second, cycling on and off treatment may be a recipe for drug resistance. Though NIAID have not detected resistance mutations in study participants, this may be regimen-specific, and might not be the case if efavirenz or nevirapine-based regimens, (or any which involve drugs which are eliminated from the body slowly), were stopped abruptly. Finally, though reductions in the amount of HAART prescribed might produce immediate cost savings, treatment interruptions may not prove cost effective if they result in treatment failure and ill health.

However, the possible advantages of cycled therapy are such that study in this area is sure to be pursued. In fact some treatment activists are frustrated by the pace of STI research. Richard Jeffreys, of New York's AIDS Treatment Data Network, told *AIDS Treatment Update*: "It's become almost a mantra for

[researchers] to say "structured treatment interruptions should only be attempted in closely monitored clinical trials". This is entirely laudable, but while people are clamouring to join such studies, the only ones open for enrolment that I am aware of are at the [US] National Institutes of Health".

"Presumably there are smaller ongoing local studies, but it is totally frustrating for people to read these statements and then call their local AIDS organisation only to find that there is no 'closely monitored clinical trial' in which to enrol. It is perhaps not surprising that people end up ignoring the oft-repeated advice to 'not try this at home'."

IMMUNE-BASED TREATMENT

A further potential HAART-sparing strategy is the use of therapies designed to boost the immune system, and thereby postpone (or even avoid) the need to intervene with antiretrovirals. The two candidates which have been best studied so far are interleukin-2 (IL-2), and *Remune*. Both of these treatments are under investigation as *additions* to HAART as well.

In Durban, Mike Youle of the Royal Free Hospital, London, presented data from an IL-2 study which was run in London and Brighton⁴. IL-2 raises CD4 counts though activating the immune system, but it has been a concern that this activation could also cause an increase in HIV replication, particularly in the absence of effective anti-HIV therapy. To investigate this further, Mike and colleagues randomised 36 antiretroviral naïve people to receive either no treatment, high dose IL-2 (7.5MIU twice daily), or low dose IL-2 (4.5MIU twice daily). IL-2 was given by injection, under the skin, in cycles lasting five days, every eight weeks for a period of 24 weeks. At entry, all participants had a CD4 count over 350 cells, the median count was 440 cells, and the median viral load was 20,000 copies.

Five people had left the study by 24 weeks, two of whom had been randomised to IL-2 but had not started treatment. At this point, CD4 counts were significantly higher in the IL-2 recipients than in the control group, rising by 148 cells on average compared to 25. There was no difference in viral load levels between the different arms at any time during the study, suggesting that whilst IL-2 increased CD4 counts, this had not been at the expense of stimulating viral replication. IL-2 is associated with unpleasant side-effects during treatment cycles, however, and these were more severe at the higher dose.

The real question regarding IL-2 use is whether the boosted CD4 counts which tend to accompany its use – with or without

FURTHER READING

For more information on the treatments and strategies discussed in this article, follow the Treatments link at aidsmap.com

ESPRIT TRIAL

The ESPRIT study is an international trial investigating the long-term effects of IL-2, with HAART, on health and survival. It is planned to run for over five years and is soon to be recruiting at sites in the UK. For details see aidsmap.com, or the ESPRIT website: <http://www.espritstudy.com>

antiretrovirals – reflect a genuine improvement in immune function. Critics suggest the increase may constitute a redistribution of existing cells that may not significantly benefit health over the longer-term. These ‘clinical’ factors are under investigation in two large IL-2 plus HAART studies which are currently recruiting (ESPRIT and SILCAAT, see sidebar for more details), but their results will not be available for several years yet.

Similar criticism is levied at *Remune*, a therapeutic vaccine made from inactivated HIV, which is designed to stimulate improved immune control of HIV in people who are HIV-positive. Whilst new data from a Thai study investigating *Remune* without anti-HIV therapy in people with no experience of antiretrovirals were presented in Durban⁵, they did not clearly demonstrate that *Remune* has a useful role in this context. Further study is needed to prove that *Remune* produces lasting health benefit rather than a knee-jerk reaction from the immune system.

DELAYING TREATMENT

A third strategy to reduce the harmful effects of HAART is simply to start taking treatment later in the course of disease. The best time to begin anti-HIV therapy is one of the great unknowns of HIV medicine. Whilst UK treatment guidelines advise beginning before the CD4 count falls below 350, and US Federal guidelines adopt a higher level of 500 cells, these cut-offs are based on guesswork rather than proof. There is no robust evidence that delaying treatment until CD4 counts have fallen into the 200 to 350 cell range will result in more illness and an increased risk of death. In fact, data from a large group of European patients, reported in *AIDS Treatment Update* issue 84, found no clinical advantage to starting treatment above 200 cells.

In Durban, a similar analysis of Canadian patients was presented, illustrating the emerging trend towards re-appraising the ‘Hit Early’ approach to HIV treatment⁶.

The Canadian study group included all those people who had begun three drug antiretroviral combinations between August 1996 and September 1999 – 1,353 in all. 134 of these were excluded from the analysis because baseline viral load or CD4 results were not available. HAART was begun at an average CD4 count of 280 cells and viral load of 120,000 copies.

Neither viral load, having an AIDS diagnosis, or taking a protease inhibitor were found to predict survival. Instead, the CD4 count was found to be a much stronger influence, and the effectiveness of HAART on

survival was compromised only where treatment began at counts below 200 cells.

However, these data are observational and so are more open to bias than the results of randomised trials. Also, the study looked only at risk of death, and not ill health. Most importantly, the short follow-up period, a median of 20.2 months, is not long enough to capture the longer-term picture.

Clearly, the use of any treatment which is not clinically indicated represents an economic burden at the societal level and a burden on quality of life at the individual level. Given the heightened sensitivity to discrepancies in treatment access between rich and poor which was evident in Durban, calls for those who advocate early treatment to produce unambiguous evidence of its worth seem particularly timely.

Key conclusions:

- ◆ Current anti-HIV therapies have had a profound effect on the health and survival of people with HIV in richer nations.
- ◆ Concern over their long-term harmful effects, their demands in terms of patient adherence, and their cost, has led some researchers to investigate treatment strategies which reduce the use of HAART.
- ◆ Potential cost savings mean these strategies may be useful in resource-poor settings.
- ◆ The effects of cycling treatment are not well understood and may result in the loss of benefits gained through use of HAART. Our understanding will only change after the completion of large, robust trials.
- ◆ Immune-based treatments, taken with or without HAART, appear to raise CD4 counts, but whether this will translate into improved health and survival is not known. They do not seem to have a detrimental effect on viral load.
- ◆ The best time to begin HAART is not known, but there is little clear evidence that beginning treatment at higher CD4 counts results in better health and survival than waiting until the risk of HIV-related illness is more profound, because this issue has not been adequately studied.

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Next generation

Durban provides encouraging data on new drug options

BY ROBERT FIELDHOUSE

Data presented at the International AIDS Conference in Durban on Abbott's unlicensed protease inhibitor ABT-378/r (lopinavir) have provided further insight into the potential usefulness of the drug in people with and without antiretroviral experience^{1,2}.

ABT-378/r IN NAÏVE PATIENTS

Data out to 72 weeks for 100 treatment naïve individuals appear impressive. Of those patients who remained on the therapy for the entire 72 weeks of study, 96% (82/84) had viral load below 50 copies at this point. According to the stricter intent to treat analysis, where data from all participants were included 81% (81/100) had viral load measurements below 50 copies at 72 weeks.

ABT-378/r IN PI EXPERIENCED PATIENTS

The 70 participants in the first of two ABT-378/r trials in treatment experienced patients, had used one protease inhibitor but were NNRTI-naïve. The NNRTI they received along with ABT-378/r was nevirapine, and the regimen also included nucleoside analogues.

At 72 weeks, 69% (40/58) of patients remaining on treatment had viral load below 50 copies. When data from the entire 70 patients were analysed, the proportion with a viral load below 50 copies was 57% (40/70). The most frequently reported adverse events were diarrhoea, nausea, fatigue and headache. The risk of rises in blood fats (lipids) on ABT-378/r increased if abnormalities in total cholesterol or triglycerides had been present at the outset of treatment. In this study, and that noted above, fifteen patients required treatment with lipid lowering drugs. Discontinuation of treatment due to side-effects occurred in four patients.

AFTER MULTIPLE PI EXPERIENCE

In a separate study, in people with multiple protease inhibitor experience, ABT-378/r was combined with the NNRTI efavirenz, plus nucleoside analogues³. Efavirenz has been shown to lower levels of some drugs in the blood, and its potential to decrease ABT-378/r levels was first reported in March. Two different doses were evaluated. In total, 57 patients were enrolled and received either three capsules of ABT-378/r (400/100mg) or four capsules (533/133mg) twice daily in

addition to once daily efavirenz plus nucleoside analogues.

All patients had used at least two PIs, either sequentially or concurrently for at least three months each (the average number was three). All were NNRTI naïve, making it difficult to assess the effect of ABT-378/r above that of the NNRTI.

On entry to the study, 68% of patients were resistant to at least three PIs, and 43% of patients demonstrated at least a 10-fold loss of susceptibility of ABT-378/r relative to wild-type virus. In this study, resistance was defined as at least a four-fold loss of susceptibility of ABT-378/r. ABT-378/r is known to boost drug levels thirty times above the level needed to control replication of wild-type virus, however. When combined with efavirenz, the more effective dose of ABT-378/r was the higher one (four capsules twice daily), since blood levels of this combination were equal to ABT-378/r without efavirenz.

At 24 weeks, 82% of patients taking the higher dose of ABT-378/r had a viral load below 400 copies according to the intent to treat analysis. Four patients discontinued treatment due to side-effects (for the same reasons as the studies featured above). Increases in triglycerides were seen in both dose arms in over one third of patients.

ABT-378/r is unlicensed at present, but is available in the UK through participation in a trial comparing the drug against other protease inhibitors, and through a named patient scheme. More details are available on the NAM/BHIVA website aidsmap.com.

AMPRENAVIR

Glaxo Wellcome's protease inhibitor, amprenavir, received a positive opinion from the European Medicine Evaluation Agency (EMA) at the end of June, though the EMA approved it only for the "treatment of protease inhibitor experienced HIV-1 infected adults and children above the age of 4 years", noting "the choice of amprenavir should be based on individual viral resistance testing and treatment history of patients". They issued a caution about its use in PI-naïve patients stating that it is "less effective than indinavir", and its use in heavily pre-treated PI-experienced patients, where it "has not been sufficiently studied".

Amprenavir appears to have a different resistance profile to other protease inhibitors,

ABT-378/r IN CHILDREN

ABT-378/r is also being studied among both treatment naïve and NRTI/PI experienced children between three months and twelve years⁴.

Whereas naïve patients received triple therapy consisting of ABT-378/r, d4T and 3TC, experienced patients also received nevirapine. At 24 weeks 82% of treatment naïve children had a viral load below 400, compared to 66% of treatment experienced children. The proportion below 400 copies at 24 weeks decreased from 72% when only NRTI had been taken previously, to 58% in children had experienced both a PI and NRTIs.

and this is the basis for its use as a second-line PI. The daily pill burden is high (eight large capsules twice daily), and it cannot be taken with high fat meals. It seems not to be the easiest drug to tolerate; one study found that 30% of people on AZT/3TC/amprenavir developed nausea, 10% experienced vomiting, and 18% developed a rash. Taking amprenavir with a small amount of ritonavir, to boost blood levels and reduce the pill burden, is under investigation.

For people selecting a second-line PI, amprenavir and ABT-378/r are apparent alternatives, but there are no clinical trial data available to indicate which would be the better choice.

T-20

The first of an entirely new class of drugs called fusion inhibitors, T-20 has now been studied for 48 weeks among a highly treatment experienced population⁵. The median number of prior antiretrovirals used was nine, and median viral load was 100,000 copies, with CD4 count at a median of 90 cells – a highly experienced and advanced group of patients.

T-20 needs to be administered by injection under the skin twice daily. The most reported adverse event, experienced by 71% of participants, remains injection area reactions. Forty one patients of the 71 who had enrolled, completed 48 weeks of the study. The other 30 discontinued for a range of reasons, fourteen due to virological failure, three due to adverse events not related to T-20, and seven withdrew voluntarily.

Of the 41 patients remaining on T-20, 22% had a viral load below 50 copies, 39% were below 400 copies, and 61% maintained a viral load that was at least one log below their baseline level. When data on all participants regardless of whether they completed 48 weeks were included, the percentages had declined to 13%, 23% and 33% respectively.

It is impossible to determine the direct effect of T-20 on viral load because of the number of additional drugs taken alongside T-20, the median number being five. Those with least drug experience, and those able to add a new class of drug are likely to have gained the most benefit.

Phase III trials of T-20 are expected to begin in the US and Europe over the coming few months.

TRIZIVIR

Glaxo Wellcome also received a positive opinion on its triple nucleoside analogue, one pill combination *Trizivir* (AZT, 3TC, abacavir)

from the EMEA at the end of June. This means that *Trizivir* will be available for marketing in Europe by October.

All three components of *Trizivir* are already licensed, so this is a new formulation rather than a new drug. The EMEA committee noted that the “demonstration of benefit of *Trizivir* is mainly based on results of studies performed in treatment naïve patients or moderately experienced patients with non-advanced disease. In patients with high viral load (above 100,000 copies), choice of therapy needs special consideration”.

Previous clinical trials suggested that a combination of AZT, 3TC and abacavir is not as potent in people with a viral load over 100,000 as a PI-containing regimen. However, a study from Argentina which was presented in Durban, in which 36% of the 342 participants had a viral load greater than 100,000 copies, found that those with higher viral loads were just as likely to have a viral load below 50 copies at 24 weeks, regardless of whether they were taking *Combivir* (AZT and 3TC) with abacavir or *Combivir* with indinavir⁶. Longer follow up is needed to determine whether the triple nucleoside regimen will prove as durable as a PI-based combination in these patients. Nonetheless, the advantages of *Trizivir* are its convenient, compact dosing (one pill twice daily) and its lack of liquid and dietary restrictions.

A number of studies are investigating the effects of switching to *Trizivir* whilst viral load is undetectable, with the aim of improving tolerability whilst maintaining virological control. ‘Simplification’ strategies are also being pursued using other simple regimens.

ENTERIC COATED ddl

The EMEA has also approved a new formulation of Bristol-Myers Squibb's nucleoside analogue, ddl, designed to cut down the number of tablets and make the drug easier to tolerate.

The new formulation comes in a capsule to be taken once a day, at least half an hour before eating or on an empty stomach. The capsule coating protects the drug from being broken down by acid in the stomach, eliminating the need for an antacid buffer. The buffer is what makes ddl tablets bulky, and it can also cause diarrhoea and other gastrointestinal problems. Interactions between the buffer and indinavir, ketoconazole and ciprofloxacin are also eliminated in the new formulation. The encapsulation of ddl also cuts out the need to dissolve tablets in water, thus eliminating the need to taste the drug.

The new formulation, called *Videx-EC* (for enteric coated), is already available in the UK

FURTHER READING

Follow the Treatments link to *Drugs used by people with HIV* on aidsmap.com for more extensive reviews of the drugs covered in this article.

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on a named patient basis for anyone who can't tolerate the existing tablet formulation of ddl, or for anyone failing on an existing regimen, or for anyone who is starting treatment. The EMEA approval means the drug will be available on prescription throughout Europe from late September onwards. ddl is the second once-daily anti-HIV drug to be approved, following efavirenz.

The EMEA approval comes just months after BMS introduced reduced mass ddl tablets containing less buffer, so that ddl could be dosed once daily in the form of two 200mg tablets.

KEY CONCLUSIONS

- ♦ ABT-378/r is a powerful, second-generation protease inhibitor, which appears effective in both treatment naïve and treatment experienced people. Results on people treated with multiple PIs are preliminary however.
- ♦ Amprenavir is to be licensed for treatment of protease inhibitor experienced patients. Its usefulness in untreated patients is not well established.
- ♦ T-20 is a completely new type of anti-HIV drug which is soon to enter later stage trials, and may also be useful in people with heavy drug experience.
- ♦ The licensing of *Trizivir* marks a step forward in simplifying treatment regimens. Such simplifications may result in improved adherence. Triple nucleoside analogue regimens, like *Trizivir*, may not be the best choice for people with high viral loads.
- ♦ A new capsule formulation of ddl has also been approved, and will make this drug easier to take.
- ♦ Adding a new class of drug, when switching treatment, remains desirable.

NEWS IN BRIEF

Viral load blips

According to data from two American studies of people on HAART, temporary increases in viral load to just above undetectable levels (called viral load 'blips'), are not uncommon, and they do not raise the risk of loss of virological control.

241 people receiving AZT/3TC/indinavir, who had suppressed viral load below 50 copies after 24 weeks of treatment, were followed for 60 weeks. Between weeks 24 and 60, 40% had intermittent blips over 50 copies, and 20% above 200 copies. 10% had more than one viral load result above 50 copies, and 13% had two consecutive results above this level.

More often than not, however, blips in viral load returned to undetectable levels subsequently, and were not associated with an increased risk of virological failure. 9 of 96 blippers, and 20 of 145 people who maintained uniform suppression below 50 copies, experienced viral rebound, (defined as two consecutive viral load measurements above 200 copies). There was no difference in risk between the two, and no difference in the time before virological failure occurred.

A second study involving 342 people followed in a clinical setting reported similar results. Of

these, 32 people had viral load results below 50 copies on two tests during a four month period, but then subsequently blipped between 50 and 400 copies. Three quarters of these had viral load back below 50 copies on their next test.

These studies support existing treatment guidelines which advise a repeat test if viral load becomes detectable. Changing treatment after one blip, however, may well be unnecessary. (Reference: 13th International AIDS Conference, abstracts TuPeB3195, MoPpB1019).

Indinavir/ritonavir

The discovery that a small dose of ritonavir, taken with indinavir, can allow indinavir to be taken in two daily doses rather than three, has encouraged many indinavir users to alter their regimen accordingly. For most people, twice daily regimens fit more easily into daily life than those taken three times a day. Aside from this, the addition of ritonavir to indinavir allows the stringent dietary restrictions which apply when indinavir is taken without other PIs, to be disregarded, and this is another welcome change.

However, our understanding of the longer term effects and safety of indinavir/ritonavir with indinavir alone has necessarily been

limited, and amongst a range of possible dosing regimens under investigation, it has not been clear if one is superior to the others.

The BEST study randomised 326 people taking three times a day indinavir (plus nucleoside analogues) to either remain on that regimen or switch to twice daily indinavir (800mg) plus ritonavir (100mg). All had viral load below 500 copies at entry, and median CD4 count was around 420 cells.

In the 237 people followed for 24 weeks, there was no difference in virological response between the two arms. However, toxicity was greater amongst the ritonavir recipients, who were more likely to stop treatment because of side-effects, and to experience moderate problems such as nausea or vomiting. The incidence of kidney stones, a side-effect of indinavir, was also greater in those switching to indinavir/ritonavir, underscoring the need for continued intake of fluids.

Dosing each drug at 400mg twice daily is another alternative. Because this regimen results in lower peak levels of indinavir in the blood, (the highest level indinavir reaches after a dose is taken), it is considered less likely to cause kidney stones. This improvement may come at the cost of a greater risk of experiencing ritonavir-related side-effects however.

The pill burden is also slightly higher than for the 800mg/100mg regimen (5 pills twice daily vs three pills twice daily). Whilst people switching from three times daily indinavir to twice daily indinavir (400mg) plus ritonavir (400mg) reported finding the new regimen easier to take and missed fewer doses, the risk of stopping treatment was high. Discontinuations in the first month of this study, most of which were due to side-effects, occurred in 21% of 301 people adding ritonavir and 15% of 79 people remaining on three times daily indinavir.

Though there is little evidence that once daily regimens are easier to follow than those taken twice a day, doctors in Italy are investigating an indinavir (1200mg) plus ritonavir (100mg) regimen which is taken once daily. Early follow-up of twelve people with viral load well suppressed below 50 copies on a three times daily indinavir regimen found no loss of virological control. Kidney stones occurred in two however, the result of higher indinavir peak levels. (Reference: 13th International AIDS Conference, abstracts WeOrB484, WeOrB482, TuPpA1155).

How many pills?

Analysis of results from 23 clinical trials investigating HAART use in people new to anti-HIV therapy found a striking association between the number of pills prescribed and viral load response at 48 weeks.

The total sample amounted to 3,257 people, who between them took nineteen different regimens, including protease inhibitors, NNRTIs and triple nucleoside combinations. On average, 47% had viral load below 50 copies after 48 weeks of treatment. Viral load or CD4 count on starting treatment were not found to predict virological success, but there was an association between pill count and having viral load below 50 copies at week 48 – the greater the number of pills, the lower the chance of a good response.

Whilst more compact regimens have been in favour for some time, this finding may be of greatest relevance in the design of clinical trials. 11 of the 23 studies included in this analysis were blinded, meaning that as well as the active treatment allocated, participants also took matching placebos of treatment in the comparison arm. This practice, though in many ways the most rigorous way to compare treatments, can push up the pill count considerably and cannot be expected to mirror 'real-world' treatment use. (Reference: 13th International AIDS Conference, abstract ThPeB4998).

Zyban & HAART

Zyban, a new anti-smoking treatment, may interact with anti-HIV therapies. *Zyban*, also known as bupropion, has not been thoroughly investigated in people taking antiretrovirals as yet, but its common metabolism through the P450 enzyme system in the liver means that interactions with certain drugs are likely. People taking *Zyban* with anti-HIV therapy should discuss the potential for interactions with their doctor or pharmacist.

The drug is contraindicated with ritonavir, and according to drug interaction experts at the University of Liverpool, its use should be closely monitored when it is taken alongside other protease inhibitors, or NNRTIs, as a change in dosage (most likely of *Zyban*) may be required.

Zyban is not nicotine-based and differs from other options currently available for those who want to quit smoking. Bupropion is an antidepressant marketed by Glaxo Wellcome as *Wellbutrin*. *Zyban* is also produced by Glaxo Wellcome.

GLOSSARY OF TERMS

adherence The act of taking a treatment exactly as prescribed

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

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

clinical outcome The occurrence of a physical symptom

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

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

immune-based therapy A substance which changes an aspect of the way the immune system is working

lipid A general term for fats in the blood

log Short for logarithm, a measurement scale often used when describing viral load

nadir The lowest point to which viral load falls after starting anti-HIV drugs

naive Never having taken anti-HIV treatment before

named patient scheme A means of access to an unlicensed drug, in which a doctor requests supplies from its manufacturer for a specific individual

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

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 The process of selecting by chance the treatment that a clinical 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

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

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

triglycerides The basic building blocks from which fats are made

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

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

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