

# AIDS TREATMENT UPDATE

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## Getting it right

**Choosing and using anti-HIV therapy: lessons from the 1999 Resistance Workshop**

BY KEITH ALCORN

Since *AIDS Treatment Update* last covered resistance testing in September 1998, you might think that great strides had been made in understanding how to use these tests to improve HIV treatment. This is not the case, as the recent International Workshop on HIV Drug Resistance and Treatment Strategies in San Diego demonstrated. Dr Charles Boucher, an organiser of this workshop attended by 200 of the top resistance researchers in the world (and a handful of community press including this writer) warned at the end of the meeting: "We need to do a lot more work before we know how to use genotypic and phenotypic resistance tests – if we just proceed on the basis that it's a good thing some patient groups might suffer".

Some doctors are proposing that resistance tests should be used before starting treatment (to determine if you already have acquired resistance to any drug); after a first regimen fails (to determine which drugs to switch to) and to determine any future regimens. At the San Diego meeting, it became clear that there's still lots of confusion about the way to use resistance testing at each of these stages.

### PRIOR TO TREATMENT

Researchers from New York caused consternation when they revealed that 12.5% of their recently infected patients already had resistance to 3TC and/or an NNRTI such as nevirapine or efavirenz<sup>1</sup>, while another US group appeared to demonstrate that 22% of recent seroconverters had resistance to NNRTIs. This led to suggestions that people starting therapy in primary infection should not use regimens which included 3TC or NNRTIs. "Rubbish", said Professor John Mellors, (who first reported the link between viral

load and disease progression risk). He pointed out the flaw in these studies: using genotypic tests, you can pick up lots of polymorphisms (naturally occurring mutations) which might contribute to high level resistance if these individuals were also to develop one of the major mutations associated with NNRTI resistance. But to say that these changes indicate 'resistance' is highly controversial. Indeed one poster at the conference showed that people who had these mutations before starting treatment didn't suffer an impaired response to efavirenz compared with those who had no polymorphisms<sup>2</sup>.

Furthermore, researchers need to be very careful measuring changes in drug sensitivity (by phenotypic testing). These tests measure how much of a drug is required to inhibit virus production; as resistance grows, more drug is needed and sensitivity is said to fall. Small changes in sensitivity to drugs which reach very high concentrations in the blood appear to have little relevance, and such changes in NNRTI sensitivity were unlikely to have much effect on response to treatment, reasoned Professor Mellors. There may be unnecessary panic over high levels of transmission of drug-resistant HIV. However, other doctors at the Workshop were less certain: some felt that although low at present, transmission rates of multi-drug

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resistant HIV in their clinic populations had begun to accelerate since late 1998, and much of the data presented were too old to reflect this.

In London, Professor Clive Loveday of the Royal Free Hospital found no primary drug mutations associated with high level resistance in 54 untreated patients<sup>3</sup>, but plenty of secondary mutations which might compromise future treatment. These minor mutations tend to amplify the effect of any drug resistance mutations that emerge.

Whilst these findings don't suggest a high rate of transmission of drug-resistant virus, they do suggest that the genetic variability of HIV is so great, it could partially explain poor responses to treatment in people who never miss medication. The virus population in some people may be more predisposed to develop resistance when it is exposed to drugs because of these pre-existing mutations.

Commenting on the role of resistance testing prior to treatment, Dr Martin Fisher of the Royal Sussex and County Hospital, Brighton, said "What we need is UK surveillance figures from documented new infections, and also data on treatment response in naïve individuals harbouring resistance mutations".

## A REALITY CHECK

Another presentation also indicated how careful researchers have to be with resistance tests. The ENVA-2 study compared the results of genotypic testing from a standard batch of samples sent out to 56 labs worldwide<sup>4</sup>. This study found that only half of the laboratories were able to detect at least nine of the ten samples which had a 50% mutant virus population (often a blood sample taken in the clinic will contain a mixture of drug-resistant and wild-type viruses). When the level of mutant viruses within a sample fell to 25%, only one third could detect nine out of ten.

These findings suggest a high rate of variation in results of tests, and considerable difficulty in detecting low-level or emerging resistance. Detecting resistance when it is still at a low level is probably beneficial to future treatment prospects. This study suggests that it may be particularly problematic to compare resistance data between different labs at the moment, so if resistance testing does become more widely available, individuals should make sure it is done at the same centre every time, preferably one with lots of experience in doing the tests, said Professor Loveday.

Commenting on current practice at St Thomas's Hospital, London, Dr Barry Peters said "We emphasise to patients that resistance testing, and our ability to interpret it, has not

come of age. Until these problems are sorted out our efforts are being concentrated on adherence policies."

## SWITCHING TREATMENT

Despite these disturbing findings about the accuracy of resistance testing, two prospective, randomised studies (both of which have previously reported early results), suggested that resistance testing may be beneficial to some people who need to switch treatment.

In the CPCRA GART study<sup>5</sup>, people experiencing viral load rebound were tested whilst still on the failing regimen and then given a new combination based on the results

*"Resistance testing, and our ability to interpret it, has not come of age."*

*- Dr Barry Peters.*

of the resistance test. A resistance expert made the recommendation about which drugs to choose (though some doctors went on to decline this advice). This group were compared with a control group who switched treatment without information from a resistance test.

After eight weeks on the new regimen, those who had switched to a new regimen chosen using the results from a resistance test had viral load -1.2 log below baseline, compared with a -0.6 log fall in those whose doctors decided which drugs they should take without this information. However, even in the genotype arm viral load was beginning to rise again after 12 weeks, showing that "even with genotyping, it's very difficult to get more than 30-40% below the limit of detection with current drugs" said study presenter John Baxter.

Another study in France called VIRADAPT<sup>6</sup> followed patients using a similar protocol, but was able to report 48 week follow-up data. After the first 24 weeks of the study those who received genotypic resistance tests had viral load -1.2 log below baseline, compared with a -0.7 log decrease in the no-test group. At this stage everyone in the no-test arm was offered a genotypic test and switched to new drugs on the basis of the test results; 30 of 43

## ERA STUDY

The UK Medical Research Council and NHS Executive, North Thames are considering a proposal for a trial evaluating resistance testing in people who have failed therapy and have a viral load above 2,000 copies. The trial will address two questions that have not been addressed in previous studies: the utility of genotypic resistance testing in people who are not heavily pre-treated; and the utility of phenotypic resistance testing in addition to genotypic resistance testing in people with limited treatment options.

did so. After six months follow-up, viral load in this group had fallen a further 0.4 log. 30% in both groups had undetectable viral load.

Whilst these results have been cited as proof of the value of genotypic testing, some would argue that if 70% of those who switched on the basis of genotypic data have detectable viral load twelve months later, then genotypic data might not greatly enhance one's chances of staying undetectable after switching therapy. On the other hand, maintaining undetectable viral load may not be a realistic goal in salvage therapy, and any response may be better than none in this situation.

A weakness of the VIRADAPT study is that it jumbles together people who have taken one regimen with those who have taken two or more. There might be circumstances in which genotypic testing is especially beneficial, but the VIRADAPT study wasn't large enough to expose any differences. The CPCRA study on the other hand was able to show that it made no difference how many regimens had been taken prior to switching: genotypic testing was still beneficial over the short follow-up period.

## PLASMA LEVELS OF DRUGS

Further analysis of the VIRADAPT study suggests that drug level monitoring may be valuable when used alongside genotypic testing<sup>7</sup>. Individuals who maintained optimum levels of drug in their blood on at least four out of six hospital visits (and who switched on the basis of genotypic testing) had significantly lower viral load after a year than gen-switched individuals who had sub-optimal levels of drug in their blood at least twice in six months. As this study didn't include any means of monitoring adherence, we don't know why people had low blood levels.

Several researchers at the Workshop argued that the major drawbacks of current regimens (apart from the number of pills, toxicity and cross-resistance) were the dosing schedules and limited margin for error in preventing drug levels from falling below the effective level. Abbott Laboratories researcher Dale Kempf argued that their new drug, ABT-378, is showing good preliminary results because there is little danger the drug levels will tail off below the effective level if one dose is taken late or missed. Du Pont make the same argument for efavirenz, which may persist for several days at effective levels after treatment with the drug is stopped.

## HOW MUCH ADHERENCE IS ENOUGH?

Professor Roy Anderson of Oxford University pointed out that if drug levels hover around the effective level most of the time, small changes due to missed doses or alterations in

the way the drug is being metabolised can have a very great impact<sup>8</sup>. He demonstrated a mathematical model which showed that if half a drug is eliminated from the circulation within four hours (which is the rate at which indinavir is cleared), the likelihood of resistance is 100% if dosing is interrupted. In contrast, a half-life of 12 hours is associated with a 1% risk of resistance if dosing is interrupted.

Nevertheless, people do suffer viral rebound on efavirenz, nevirapine and ddI, drugs with long half-lives, and such models don't accommodate individual variations in the way that drugs are processed. All these factors make it very difficult to say how much adherence is good enough because the necessary level of adherence will vary from one regimen to another (and from one individual to another depending on individual quirks in drug processing and body mass).

There were no reported investigations into levels of adherence and the development of drug resistance at the Resistance Workshop. However, at a conference in Canada three weeks later one group reported that adherence levels of 91% or greater were the best predictor of long-term viral suppression below 50 copies<sup>9</sup>. In those with viral load hovering between 50 and 500 copies, adherence averaged 79%. Adherence levels were assessed by patient self-report. However, this marginal difference (missing two doses out of ten rather than one dose out of ten) was enough to compromise viral suppression and increase the risk of resistance. It also suggests that efforts which result in marginal improvements in adherence may still influence long-term treatment outcomes.

## HOW DURABLE IS A GOOD RESPONSE?

The longer you stay undetectable on HAART, the lower your risk of viral rebound, reported Professor Andrew Phillips of the Royal Free Hospital<sup>10</sup>. He analysed 406 drug-naïve individuals who started a three drug regimen containing two NRTIs plus either a PI or an NNRTI, with an average viral load of 250,000 copies before starting treatment. 91% went below the limit of detection within 24 weeks, with a decreasing risk of viral rebound for each year on therapy. The risk of viral rebound was much greater during the first year below the limit of detection than subsequently (21% vs. 7% in the second year).

If current trends within this group continue, Phillips estimated that some individuals could expect to sustain undetectable viral load on their current regimen for at least 12 years. This study emphasises the huge importance of getting it right when starting treatment, and the need for people on therapy to be closely monitored and supported.

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# Body fat changes

## Possible d4T link confuses search for cause and treatment

BY KEITH ALCORN

Evidence that d4T (stavudine, *Zerit*) may contribute to the body fat changes seen frequently in people on antiretroviral treatment was presented at an international workshop on side-effects of anti-HIV drugs in June.

Until now it had been thought that protease inhibitors (PIs) might be solely responsible for the fat redistribution in people receiving HAART, but the First International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV Infection, held in San Diego, heard that fat loss is also being seen in some people who have never taken PIs.

Five cohort studies from France<sup>1</sup>, Italy<sup>2</sup>, Australia<sup>3,4</sup> and the US<sup>5</sup> found a significant association between d4T treatment and fat loss from the face, arms, legs or buttocks. Two of these studies, from the US and Australia, found that the length of time on d4T increased the risk of fat loss (though the US study also found duration of indinavir use to be a predictor of fat redistribution).

One of the Australian teams reported that 14% of 66 people who had never taken a PI had fat loss, compared with 51% on PIs who had experienced fat loss<sup>4</sup>. They found that each year of d4T treatment increased the risk of fat loss from the arms or legs by 256%. A second group in Sydney found 14 out of 44 individuals who had never taken a PI (but with an average 61 months on NRTI dual therapy) had fat loss in the face, arms, legs or buttocks. Only d4T and increasing age were statistically associated with fat loss in these patients<sup>3</sup>.

However, caution is required in interpreting these findings. A report from the Aquitaine cohort from France found no association between fat redistribution and d4T use<sup>6</sup>, and a retrospective analysis of the START trial (which compared the use of indinavir with either d4T/ddl, d4T/3TC or AZT/3TC), similarly found no association<sup>7</sup>. The latter study involved a look-back on case notes rather than a physical examination or patients' self-reported changes; perhaps a relatively less rigorous way of assessing the incidence of fat changes.

Whether d4T should be viewed as a critical risk factor amongst NRTIs is unclear. In the Italian study all nucleoside analogues were implicated to some extent; and a further Spanish study found that taking 3TC was also associated with fat loss<sup>8</sup>. One of the Australian cohort studies found that length of time on AZT was also linked to risk of fat loss<sup>4</sup>.

The Italian report<sup>2</sup> on 191 people who had never taken a PI found fat loss in these

proportions of people taking various drugs in the NRTI class: 26%, 18%, 16%, 9%, 9% for d4T, 3TC, ddC, ddl, AZT respectively. The combination of d4T and 3TC was most strongly associated with fat redistribution. Fat changes were also more common in women than in men.

Though the Sydney-based cohort study reported above linked fat loss with d4T use, their analysis of fat gain suggests that central obesity (fat stomach) and buffalo hump were associated with duration of either PI therapy or 3TC treatment<sup>3</sup>.

150 Spanish patients taking indinavir with either AZT/3TC, d4T/3TC or d4T/ddl were recruited to assess fat loss over time, and the potential link between NRTIs and PIs<sup>8</sup>. At baseline, the frequency of lipodystrophy was already variable, from 2% of those receiving AZT/3TC/indinavir, to 25% of those on d4T/3TC/indinavir and 65% on d4T/ddl/indinavir. Proportions with lipodystrophy six months later were unchanged in the AZT/3TC group, but had increased to 52% in the d4T/3TC group and 88% in those on d4T/ddl.

### A POSSIBLE MECHANISM?

The mechanism by which d4T or other nucleoside analogues might cause fat loss is unclear, though a theory was advanced at the Lipodystrophy Workshop<sup>9</sup>. Mitochondria are found in cells in body tissues and turn sugar into energy for these cells. Mitochondrial DNA is easily damaged by nucleoside analogues (with the exception of 3TC), and when it is damaged, cells may die. Why fat cells in the limbs might be particularly affected by d4T is unclear. One suggestion is that nucleoside analogues may damage the DNA of mitochondria in adipocytes (fat cells) that store fat in the limbs. This would eventually lead to the death of adipocytes in these areas resulting in a loss of fat. A very rare form of lipodystrophy, called Madelung's Disease, seen in HIV-negative people is related to mitochondrial DNA damage.

### OTHER VIEWS

Another explanation offered is that the association between d4T treatment and fat loss may be a surrogate marker for length of time on therapy, or duration of HIV infection. One study found that people with higher CD4 counts when starting therapy were at lower

#### FURTHER READING

A full review of the lipodystrophy syndrome, including theories on causation and research into its management can be viewed on the NAM BHIVA website at <http://www.aidsmap.com>

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risk of experiencing fat loss<sup>3</sup>, but not every cohort study investigated this potential link. If this were the case, it is not surprising that d4T has been more strongly linked to fat loss than AZT or other NRTIs, because d4T is now more widely prescribed than AZT, and has been for several years. People who started therapy after 1996 were more likely to start with a d4T-containing regimen (prior to the introduction of *Combivir*), and people who had taken dual combinations prior to 1996 were likely to switch to d4T upon beginning PI therapy in 1996/97 – for many people AZT and d4T have been used sequentially.

Moreover, some of this new research has come from cohorts of people who have been (and continue to be) treated with dual NRTI regimens. This form of therapy is rarely used today, and is generally not recommended because it is unlikely to sustain suppression of viral load over the long-term. The minority of people who do respond well to dual NRTI therapy may be over-represented in these cohorts. In other words, it's possible that some other common characteristic may be introducing a degree of bias.

## DROPPING D4T

Nevertheless, two small switching studies provided intriguing evidence that d4T is contributing directly to fat loss. Ten Spanish patients who were switched from d4T/ddI to AZT/3TC showed significant improvements in body fat distribution after 12 weeks<sup>8</sup>.

Fourteen French patients on stable NRTI therapy, and fifteen who were receiving a PI-containing regimen, discontinued d4T<sup>10</sup>. In the NRTI group, average abdominal and mid-thigh sub-cutaneous fat increased by 41% after six months off the drug. PI recipients experienced a 27% increase in abdominal sub-cutaneous fat, and a 41% increase in mid-thigh sub-cutaneous fat.

## OTHER FACTORS

It has been clear for some time that the body fat changes seen in people on HAART fall into three distinct patterns: fat loss only, fat gain only, and a mixture of the two. Whilst several studies have now linked d4T to fat loss, no particular factor has been linked to fat gain.

It has been suggested that PIs, either alone or through interaction with nucleoside analogues, might kill fat cells, driving up triglycerides and hence insulin resistance, which in turn leads to the accumulation of central visceral fat. Triglycerides would be re-directed towards central fat storage rather than sub-cutaneous fat.

Two studies at the conference showed that protease inhibitors reduce the number of

insulin receptors in the muscles (more severely than in diabetes), and directly affect insulin production in the beta cells of the pancreas<sup>11,12</sup>. However, insulin resistance was seen in approximately 25% of people on NRTIs, but not in any treatment naïve individuals. There was no significant difference between the incidence of insulin resistance in people taking PI-containing regimens and NNRTI-containing regimens (55% and 50% respectively). These data suggest that something to do with antiretroviral treatment, rather than HIV infection or any specific drugs, is responsible for the shift to a pre-diabetic state. However, this does not prove that insulin resistance causes the body fat changes.

## HOW CAN FAT CHANGES BE TREATED?

Given the lack of clarity about what causes the syndrome, it is impossible to give advice at the moment about how to avoid it or how to treat it. For example, if d4T or other NRTIs are indeed involved in its cause, then switching to a PI-sparing regimen whilst maintaining an NRTI backbone may not solve the problem, and mars the interpretation of switching studies which have been reported.

Spanish researchers randomised 64 individuals receiving d4T/3TC/PI to switch to d4T/ddI/nevirapine or to remain on d4T/3TC/PI<sup>13</sup>. Improvements in body shape were observed amongst the nevirapine group after 12 weeks, but whether this was due to the replacement of the PI with nevirapine, or of 3TC with ddI, or both is unclear.

Research from another Spanish group suggests that 12 weeks follow-up may be too short. 23 individuals with fat redistribution were switched from a PI-containing regimen to a nevirapine-containing regimen, but fat distribution had not returned to normal after a year<sup>14</sup>. In both studies there were significant improvements in blood lipid levels.

Dr Graeme Moyle of the Chelsea and Westminster Hospital reported on 11 people with lipodystrophy who switched from a PI to efavirenz<sup>15</sup>. After 12 weeks, visceral fat had fallen by just 0.5% on average, and mean cholesterol and triglycerides had risen. Lipid levels began to fall back towards the levels seen on previous PI treatment after 24 weeks. In Paris, 31 people switched from a PI to efavirenz. After three months, one patient reported partial improvement of fat loss in his arms, but no other improvements were noted<sup>16</sup>. Lipid levels did not improve.

These changes compare unfavourably with those seen in people treated with human growth hormone<sup>17</sup>. 30 people with increased visceral fat were treated for three months. Visceral fat fell by 50%, whilst triglyceride levels fell and insulin sensitivity improved.

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# Lipodystrophy

However, an earlier attempt to reduce buffalo hump and abdominal fat using human growth hormone found improvements were not sustained once treatment was stopped (see *AIDS Treatment Update* issue 75). Human growth hormone is not currently available to treat lipodystrophy in the UK, (though trials are currently taking place in the USA).

For some, a wait-and-see approach may be most suitable. At the lipodystrophy clinic at St Thomas', London, over 80% of patients have chosen to stay on their existing regimen. According to Dr Barry Peters, this is because "They know they can receive regular monitoring, and they prefer to continue with the benefit from remaining on a successful regimen, than risk problems changing drugs".

## PI-SPARING REGIMENS

In people who started treatment with efavirenz (as opposed to switching to it from another drug), rates of reported lipodystrophy were low, according to manufacturers DuPont Pharma<sup>18</sup>. 1266 people who took part in the 006 comparison of efavirenz with indinavir for at least 88 weeks were reviewed. Less than 1% of those on AZT/3TC/efavirenz had physical signs of lipodystrophy after 24 weeks, compared with 2% in the indinavir/AZT/3TC arm and 3% in the indinavir/efavirenz arm. However, it's important to remember that several cohort studies have identified duration of treatment as being significantly associated with fat redistribution, and that people in this study were new to treatment at entry.

Moreover, in common with the retrospective analysis of START (also conducted by the manufacturer of treatments under investigation), these findings resulted from the authors having "probed the database", rather than evaluated physical examinations or patient self-assessments.

A similar review of participants in five studies of delavirdine-containing regimens showed no significantly increased risk of body fat redistribution or metabolic disturbances in those who received delavirdine compared to those who received NRTIs alone<sup>19</sup>.

## CONCLUSION

Reviewing the Lipodystrophy Workshop for Medscape<sup>20</sup>, US commentator Don Kotler urged caution in responding to this new research: "While the major finding of this conference is that lipodystrophy may occur in the absence of protease inhibitor therapy, we should try to avoid the urge to find another culprit". He continued, "The ability to detect associations between possible causes and effects is related to their prevalence".

Dr Martin Fisher of Brighton's Royal Sussex and County Hospital agreed. "The real evidence will only come from long-term prospective studies. Until that time, or unless other new information becomes available, everybody taking or prescribing therapy needs to continue to consider the risk/benefit ratio of treatment versus none, PI versus non-PI, d4T versus non-d4T, which will vary from one individual to another."

## NEWS IN BRIEF

### MENINGITIS C VACCINATION

A new meningitis C vaccination programme aimed at children and young people was announced in July. This vaccine can be given to children with HIV infection.

### INFO FORUM

There will be no NAM Information Forum in August, but we return on September 20<sup>th</sup> with a discussion of the new UK guidelines on anti-HIV therapy.

## Nevirapine news

A study conducted in Ugandan women has found that one-off doses of nevirapine given to pregnant women in labour, and to the newborn child soon after birth, can reduce the rate of HIV transmission from mother to baby to 13% at 14 to 16 weeks of age.

The cost of this regimen has been calculated at \$4.00, and the US National Institutes of Health who sponsored the study, have estimated that if implemented widely in developing countries, this intervention potentially could prevent some 300,000 to 400,000 newborns per year from being born with HIV. However, the necessity for many of these children to be breast-fed means that many will become infected later in life.

The nevirapine regimen was compared with a short course of AZT given during labour, and to the infant for the first week. The

transmission rate in this arm was 25%, a rate which appears unusually high compared with other studies of short courses of anti-HIV therapy in breast-feeding women.

It is not known if the addition of nevirapine to other interventions which women may be using during pregnancy (such as combination therapy or elective caesarean section) will provide any additional benefit in terms of reducing the risk of transmission. This is being evaluated by a large US/European/South American study called ACTG 316. Because the rate of transmission is very low in women who take effective antiretroviral therapy, a very large number of women will need to be recruited to this trial in order to demonstrate any effect from nevirapine. Initial results from this study are not expected until late 2000.

More information on the US/Ugandan HIVNET 012 study can be read on the web at <http://www.niaid.nih.gov>.

## SO YOU THINK YOU HAVE LIPODYSTROPHY?

The first person to spot body fat changes is usually the person experiencing them. But not all body fat changes are lipodystrophy or lipoatrophy, and may be much more easily explained. If you notice body fat changes whilst on treatment, review this checklist before worrying unnecessarily.

### FAT GAIN

Where is the fat? If it is round the belly, is it pinchable or squeezeable? If the fat is squidgy, this is sub-cutaneous fat. This sort of fat begins to accumulate in previously slim adults after adolescence at varying rates. Diet, exercise and ancestry all play a role. Middle-aged spread usually begins after the age of 30 in men, and may have been disguised in previously symptomatic individuals by loss of appetite and low calorie intake. Weight gain after starting treatment may be caused by improved appetite or by increased calorie intake if you are eating a high fat diet alongside drugs like ritonavir or saquinavir.

If the stomach feels taut and pushed out, this is a sign that the fat has accumulated round the organs, not under the skin. This is lipodystrophy, and may cause discomfort.

In women, increased breast size is reported quite frequently as part of the syndrome. Again, remember that changing breast size is commonly experienced when women gain or lose weight for reasons unconnected to HIV.

### FAT LOSS

Where have you lost weight? If on the arms or legs, has weight been lost in the form of muscle or fat, or both? If the weight loss is fat loss, it will cause veins to stand out and

muscles to become more defined. If the fat has been lost from the buttocks, your hip measurement will be reduced, so clothes which may have been tight will feel loose. Sitting may also be uncomfortable.

If the wasting in the limbs also includes muscle loss, this could be related to an undiagnosed opportunistic infection, or reduced protein and carbohydrate intake due to drug-related diarrhoea. This weight loss may resolve if the diarrhoea can be stopped. Make sure that any persistent diarrhoea is thoroughly investigated to rule out an untreated infection.

If the fat loss is from the waist or other parts of the trunk, might this be related to reduced calorie intake due to changes in diet, or increased activity because you have been feeling better?

Facial fat loss may be the first clear sign of fat loss in some people. Particular fat pads in the lower cheeks and temples are affected. It is often difficult to assess these changes yourself, and some doctors recommend recent photographs taken in the same lighting conditions as a good test. Also, remember that a sun-tan can make bones appear to stand out and make the face appear thinner in people of Northern European origin.

### SKIN CHANGES

If you develop dry skin, is it all over or just in one place? Patches of dry skin are not unusual, and appear for all sorts of reasons in HIV infection (and in people without HIV too). They may be allergic reactions, nothing to do with HIV treatment, and may respond to *E45* or *Diprobase* cream. Dry skin, scalp and lips are reported most commonly with indinavir.

### ABACAVIR APPROVED

Glaxo Wellcome's nucleoside analogue abacavir received full approval for marketing in the European Union in July. The drug will be prescribed under the tradename *Ziagen*. Abacavir is dosed as one tablet taken twice daily, and should always be used in combination with other antiretrovirals. A review of abacavir's performance in people new to treatment appeared in *AIDS Treatment Update* issue 76. For information on abacavir in people with drug experience see issue 72.

### THANK YOU

Thanks to Roy Kilpatrick who has joined *AIDS Treatment Update*'s peer review panel. Roy is Co-ordinator of the Scottish Voluntary HIV/AIDS Forum.

### AUDIO ATU

*AIDS Treatment Update* is available on audio tape for people with visual impairment. If you know someone who would like to use this free service, contact Helen Finch on NAM on 020 7627 3200.

## NRTIs in pregnancy

In June, the UK Committee on Safety of Medicines issued guidance to NHS Trust Medical Directors concluding that the possible risks posed by the use of AZT in preventing mother-to-baby transmission were far outweighed by the benefits, after eight cases of mitochondrial dysfunction were reported in France in infants exposed to AZT, with or without 3TC, in the womb.

Earlier this year, French doctors reported the deaths of two children born to mothers who took both drugs during pregnancy. Their conclusion (which remains unproven) was that mitochondrial toxicity, a side-effect of NRTIs, had been the cause, (see *AIDS Treatment Update* 75).

## Ritonavir capsules

A new soft elastic capsule formulation of ritonavir is now available on named patient basis. This new formulation is currently under evaluation by European licensing bodies, and is expected to be approved very soon. Ritonavir users must currently take the drug in the form of a bitter-tasting liquid.

The new capsules have been designed to be bioequivalent to the old product. They contain 100mg ritonavir, and are slightly fatter and a little shorter than their predecessor. Once dispensed, they can be stored out of the fridge for up to a month (so long as room temperature is below 25 degrees). Doctors seeking information on the named patient programme should call 01628 644370.

# GLOSSARY OF TERMS

**antiretroviral** Something that attacks retroviruses such as HIV

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

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

**diabetes** A blood disorder caused when the body can't use or metabolise sugar properly. Symptoms include extreme thirst, blurred vision and frequent urination

**DNA** The chemical form in which cells store their genetic information

**genotypic test** Resistance test which detects changes in HIV's genes

**insulin** Hormone which enables body tissues to take up sugar from the blood

**insulin resistance** When insulin is present in the blood but unable to do its job properly

**lipid** A general term for fats in the blood

**lipodystrophy** A disruption to the way the body produces, uses or distributes fat

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

**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

**phenotypic test** Resistance test which measures the amount of drug needed to stop HIV reproducing

**primary infection** The first few weeks after infection with HIV

**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, zidovudine, zalcitabine, didanosine, zalcitabine, zalcitabine, zalcitabine

**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

**sub-cutaneous fat** Fat beneath the skin

**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

**visceral fat** Fat around the internal organs, particularly in the abdomen

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## ANY QUESTIONS?

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

### ◆ AIDS Treatment Project

Phoneline: 0845 9470047  
Monday & Wednesday, 6pm - 9pm  
All calls charged at local rates.

### ◆ Body Positive

Treatment Advice: Tue, Wed & Fri 2pm - 7pm  
Call Adam, Jo or Robert on 020 7287 8010 to make an appointment.

### ◆ The Terrence Higgins Trust

Helpline: 020 7242 1010 Daily 12noon - 10pm  
Treatment Support: Call the Treatments Team on 020 7831 0330 for an appointment.

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

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