



AIDS TREATMENT UPDATE

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Knowing when to stop

New research prompts warning to people on treatment: don't try this at home

BY KEITH ALCORN

One of the questions most frequently asked at NAM Information Forums and Treatment Workshops is "When can I stop combination therapy?"

Until very recently the established wisdom was that combination therapy, like a puppy, is for life. However, some researchers are now suggesting that stopping treatment in controlled circumstances may not always be harmful. In fact, it may hold the key to long-term control of HIV without the need for continuous therapy.

At last month's 6th Conference on Retroviruses and Opportunistic Infections in Chicago, Dr Franco Lori of the US-Italian research body RIGHT, presented further information about 'the Berlin patient', a man who received treatment with ddI, hydroxyurea and indinavir just after becoming infected. The man interrupted treatment twice due to other medical conditions (with a slight viral load rebound the first time), and eventually stopped altogether. When he finally stopped, his viral load was undetectable and has remained so ever since.

At the Geneva AIDS conference last July, Lori reported that no replication-competent HIV could be isolated from the lymph nodes of the patient, but further tests have revealed very small amounts. However, no viral load rebound has occurred after two years off treatment, and strong anti-HIV immune responses have been detected. Dr Lori believes that these responses may have been stimulated by a period of brief and not too high viral rebound, and have remained strong enough to control residual HIV replication when therapy was stopped altogether.

To test his theory, Dr Lori has investigated this treatment model using ddI, hydroxyurea and PMPA (a nucleotide analogue like adefovir) to treat SIV infection in three macaque monkeys. After several

treatment interruptions during which viral load rebounded, the monkeys are now off treatment again, and so far, have gone for over one hundred days without any viral load rebound.

Dr Lori's team also reported on three people who started treatment on ddI, hydroxyurea and either d4T or a protease inhibitor with viral loads ranging from 16,000 copies to 720,000 copies. All started treatment within one year of infection. Rather than having missed doses or taken what are commonly called 'drug holidays', these people followed a structured treatment pattern of three weeks on treatment, an interruption until viral load rebounded above 5,000 copies, three months on treatment, another one week interruption, and a further three months on treatment before another interruption. At each treatment interruption the time it took for viral load to rebound grew longer, leading the researchers to suggest that the immune system may be playing a role in controlling HIV.

Four people treated with AZT, 3TC and ritonavir soon after infection were studied by the Aaron Diamond Centre in New York. Researchers reported that two of the men, who had interruptions in therapy due to poor adherence, had undetectable viral load

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for 21 and 14 months respectively after stopping therapy completely. On the other hand, two men who stopped therapy abruptly after similar breaks in treatment had viral load rebounds within three to four months. Long-term undetectability and the speed of viral rebound was associated with the strength of HIV-specific cytotoxic T-lymphocyte (CD8) responses, which may have been stimulated by brief bursts of viraemia.

These studies have all looked at people or monkeys infected with HIV (or SIV) for less than one year who began treatment very soon after infection. Similar experiences in people who began treatment later have not been reported, and appear unlikely given the progressive loss of immune function seen in people with longer-term infection. In fact Dr Lori himself conjectured after a recent speech about his work given in London, that the preservation of HIV-specific immunity might be dependent on starting treatment during the short 'window period' before seroconversion. "This is experimental data which is of interest but should not lead any individual to change therapy for the moment", said Lori.

WHAT'S HAPPENING IN PRACTICE?

In other cases where people have stopped antiretroviral therapy and stayed off it for some weeks or months, viral load comes back. There has been speculation that part of the reason for this rebound is the disappearance of HIV-specific immune responses. Paradoxically, if HIV suppression is 'too successful', the HIV proteins which the immune system needs to encounter in order to programme an HIV-specific immune response may be removed. Immunologists at the Chelsea and Westminster Hospital and elsewhere are working on a variety of projects to see what HAART does to HIV-specific immunity, and how it can be assisted with substances like interleukin-2, interleukin-12 and a therapeutic vaccine called *Remune*.

However, researchers disagree about the extent to which HIV-specific T-cell responses matter. Although long-term non-progressors usually have very good HIV-specific immune responses, it is still unclear whether these are the essential mechanisms responsible for their non-progression. Their absence may be a marker of some other immune deficiency which ideally, critics argue, should be measured directly.

Long-term non-progressors are very rare. The usual response to HIV infection is for the virus to overwhelm the immune system in the first weeks of infection and delete the very cells that would normally play a key role in controlling a viral infection – cytotoxic T-cells. Researchers such as Dr Lori argue that if HIV

is successfully controlled by HAART, replication can be shut down leaving a small amount of HIV-specific immune cells ready to respond next time the virus gets out of hand.

'DANGEROUS AND MISLEADING'

In the US and Europe activists and clinicians are concerned that these new findings represent a dangerous signal to people with HIV that it may be OK, in fact even beneficial, to take short drug holidays.

Professor Tony Pinching of St Bart's Hospital, London, cautioned "The research studies being described are just that – research in progress. There is no clear indication as to whether or in what circumstances they are generalisable. Great care is needed pending further data".

Recent research at the Royal Free Hospital, London, due to be published shortly will show that in people who have low CD4 counts and high viral load before commencing therapy, an interruption of drug treatment leads to a high viral load rebound and a failure to regain viral control after resuming treatment.

Even in people who start therapy during primary infection, and who stop after one year, the response may not be good. Eight patients in the Spanish EARTH study with viral load below 20 copies after one year's therapy discontinued treatment with d4T/3TC/ritonavir. Three out of eight experienced a viral load rebound to at least half a log above their viral load level when they first started treatment, and every patient had detectable viral load within two to three weeks of stopping treatment. However, all eight saw their viral load back below 20 copies within a few weeks of resuming the d4T/3TC/ritonavir regimen.

Stopping HAART after a long period of undetectable viral load may be problematic because it could 'reset the clock' of viral clearance. Long-term protease inhibitor treatment is associated with a significant clearance of cells actively producing HIV. Stopping therapy could allow a burst of viral replication to establish new reservoirs of infected cells, rather than improving immune control of existing low levels of HIV production. This view is criticised by some as speculative however. Given that proponents of the viral eradication hypothesis now estimate that HAART must be taken for 26 years before the virus may be removed from all body compartments, a short break in treatment represents only a small proportion of this time.

Short interruptions in treatment might also encourage the development of resistance. Some drugs pass through the body more quickly than others. For example, the time taken for half the dose of efavirenz to be eliminated from the body (called the half-life)

CHICAGO CONFERENCE

The articles in this issue report back the leading stories from the Sixth Conference on Retroviruses and Opportunistic Infections held last month in Chicago. Medscape conference summaries can be viewed at <http://hiv.medscape.com/hiv>. The conference website at <http://www.retroconference.org> offers abstracts and the chance to listen to conference presentations.

is around 15 hours, and for nevirapine it's around 30 hours. People who stop taking either of these drugs will therefore still have active quantities of drug in their blood for several days after. If stopped at the same time as other drugs with much shorter half-lives, the slowly diminishing levels of efavirenz or nevirapine act as effective monotherapies. This is a risky strategy – it is well established from early research on NNRTIs that they are particularly vulnerable to the rapid emergence of resistance when taken alone.

However, a number of recent studies have shown that it is quite possible to have a viral load rebound without evidence of resistance to all the drugs being taken. In the Spanish Earth study (referred to above), there was no sign that resistance to 3TC, (which appears rapidly when the drug is taken in the presence of ongoing viral replication), emerged as a consequence of stopping treatment.

If you already have drug resistance, especially to a protease inhibitor, and you have run out of new drugs with which to construct a regimen, some people might suggest that you stop treatment altogether in order to stop the accumulation of drug resistance in your virus population. Whilst some researchers have suggested that protease inhibitor resistant virus is less harmful to CD4 cells, research presented in Chicago suggests that only saquinavir resistant virus had this effect in animal experiments. The long-term benefit of protease inhibitors in people with detectable or rising viral load may be associated with their ability to reduce rates of apoptosis (cell suicide of CD4 cells), independent of their effect on HIV replication.

A PERSONAL VIEW

Alison Gray, Treatments Officer at the Terrence Higgins Trust, recently came off treatment after two and a half years on a variety of regimens.

"I first stopped treatment two days before Christmas in 1997. I was taking d4T/3TC/ritonavir and had a constant metallic taste in my mouth. I decided that I wanted to taste my Christmas dinner, so I stopped taking ritonavir. I remember looking in the fridge at the capsules that night and just thinking "No". It wasn't a considered decision!"

Alison stayed on d4T/3TC and added nevirapine about a month later, but at this time she didn't have accurate information about her viral load because the test being used at her clinic couldn't measure her HIV strain accurately. By the middle of 1998 the new combination was showing signs of failing, and Alison decided to take a complete break.

"I made sure I got a resistance test before I stopped so I knew which drugs were failing, and if you can't get resistance testing at your

clinic yet, I would advise getting a blood sample stored that can be tested later on."

"Given my general health, which is fairly good at the moment, and my travel plans over the next few months – several trips abroad – I decided to have a rest for a few months before starting on a six or seven drug regimen. After two and half years of taking pills the psychological breathing space is important to me".

Summary:

Alison Gray's experience highlights how a decision to stop treatment might be reached for many different reasons, including:

- ♦ Planned interruptions to therapy due to lifestyle factors such as holidays or recreational drug use.
- ♦ Stopping due to side-effects or illness.
- ♦ Stopping after loss of virological control and exhaustion of alternative treatment options.
- ♦ Stopping or interrupting therapy to stimulate an immune response.

Guidance:

- ♦ If you are planning to stop for any reason, talk to your doctor first!
- ♦ It may be best to stop all drugs at the same time, not just the drug which is inconvenient to take or which is causing side-effects, though this will depend on the drugs you are taking.
- ♦ If you are stopping ritonavir and switching to other drugs you may need a 'washout' period to allow your liver to go back to normal, otherwise it may flush some new drugs out too fast.
- ♦ Although a few cases have been reported in which brief interruptions to treatment might have long-term benefit, these people all began treatment soon after infection.
- ♦ Evidence suggests that drug holidays lead most often to viral load rebound and a risk of drug resistance, narrowing future treatment options.
- ♦ If you are having difficulty remembering to take medication, talk to your doctor, an HIV pharmacist or one of the services listed on the back page as soon as you detect a problem. Don't wait for your next clinic visit to discuss problems of this sort.
- ♦ Until you are advised otherwise, missing any doses is a problem that needs to be reviewed with your doctor or pharmacist in order to work out how to avoid it in the future.

QUEST STUDY

This study is designed to assess if treatment (with *Combivir*, abacavir and amprenavir) early in the course of primary infection or recent seroconversion can lead to durable viral suppression after the drugs are stopped. The trial will also compare continuation on three drugs versus four after an initial four drug induction period. Trial sites are in Belfast, Brighton, London and Manchester. See NAM's *HIV & AIDS Treatments Directory* or our website at <http://www.aidsmap.com>

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Metabolic complications

Syndrome of blood and body fat changes still poorly understood

BY KEITH ALCORN

Reports of body fat and metabolic changes associated with protease inhibitor treatment are becoming more and more frequent, and appear to affect the majority of people who have taken a protease inhibitor (PI) for at least one year. But do these changes have a single cause, will they cause long-term harm, and are there easy ways of getting rid of them?

PHYSICAL CHANGES SEEN

- ◆ Accumulation of fat in the intra-abdominal wall leading to pot belly
- ◆ Increased waist size
- ◆ Loss of fat from arms and/or lower limbs leading to wasted appearance
- ◆ Enlarged/protruding veins in the arms and legs (possibly due to fat loss)
- ◆ Wasting of the buttocks
- ◆ Increased breast size in women and men
- ◆ Accumulation of hard fat at the back of the neck (buffalo hump)
- ◆ Accumulation of fat around the neck, chin etc and infiltration of fat into facial tissues (increased collar size)
- ◆ Facial wasting
- ◆ Hair loss
- ◆ In-growing toe nails
- ◆ Dry skin and lips

METABOLIC CHANGES SEEN

- ◆ Increases in blood lipids associated with increased risk of heart disease: LDL cholesterol and triglycerides
- ◆ Loss of glucose tolerance, leading to insulin resistance
- ◆ Diabetes

Researchers are struggling to find a clear pattern amongst the host of changes being reported. At the 6th Conference on Retroviruses and Opportunistic Infections in Chicago, a thorough review of lipid and body fat changes in people on protease inhibitors was presented by French researchers. They looked at 624 people who had taken PIs for at least 12 months (average duration of treatment was 18 months). Two thirds had taken indinavir, 21% had taken nelfinavir and the remainder had taken a dual PI combination.

85% had experienced at least one physical change since starting PI treatment. The most common changes were increased abdominal wall thickness, enlargement of veins in the legs and arms, increased waist size, wasting of the

lower limbs and/or buttocks (each reported by 38-48% of the patients). Hair loss, nail disorders and alopecia were each reported by around 15%. The researchers found three patterns of body fat changes: atrophy (wasting) (20%), fat accumulation (16%) and a mixture of the two (42%). There was no significant difference between the three groups in the amount of time they had been taking PIs. There were marked differences in blood glucose levels and insulin sensitivity.

Discussion of lipodystrophy is hampered by the lack of a clear definition for the syndrome. A wide range of physical and metabolic changes are bundled together in case reports and until now, there has been little attempt to detect different patterns.

NRTIS ALSO ASSOCIATED

Protease inhibitors are not the sole factor associated with these changes. Several clinics reported on significant body fat and metabolic changes in people who had only taken NRTIs. These included:

- ◆ Significantly higher incidence of elevated triglycerides in people taking nucleoside analogues compared to untreated people (but less frequent than in people on PIs).
- ◆ Wasting of face and limbs together with increased abdominal girth in 9 patients at the Royal Free Hospital taking AZT/3TC or d4T/3TC.
- ◆ A strong association between long-term 3TC treatment (3 years plus) and fat redistribution in women, as well as a strong association with d4T treatment.
- ◆ Length of time on d4T increased the risk of fat wasting in the limbs and face irrespective of prior treatment experience, CD4 count or viral load in a study of 43 people taking dual nucleoside combinations at a French clinic.

SO WHAT ARE THE MECHANISMS?

Some researchers have proposed that PIs have a direct effect on proteins which govern the storage and mobilisation of fat in the body. In Chicago several research groups reported effects of PIs on fat and sugar metabolism.

Lipoprotein lipase (LPL) activity is inhibited by PIs but returns within twelve hours of stopping PI dosing. LPL is vital for the correct storage of triglycerides, so depression of LPL activity might explain the large rises in circulating plasma

FURTHER READING

The issues raised in this article have been reported previously in *AIDS Treatment Update*.

See: Wasting, metabolism and lipodystrophy (issue 68); Metabolic concerns (issue 67); Lipodystrophy update (issue 64); New protease inhibitor side effect (issue 61/62).

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Research discussed here was presented at the Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, 1999. See the following abstracts: Gharakhanian, 642; Thompson, 649; Madge, 654; Gervasoni, 660; Saint-Marc, 653; Baril, 664; Lenhard, 665; Walli, 645; Glesby, 650; Grunfeld, S3; Carr, 668; Moyle, 669; Ruiz, LB-14; Martinez, 670; Torres, 675.

triglycerides seen soon after starting PIs.

Retinoic acid signalling is disrupted by ritonavir, saquinavir and nelfinavir, but not by indinavir or amprenavir. Retinoic acid signalling is another component governing the storage of triglycerides. However, triglyceride increases are also seen with indinavir treatment, so this finding may not be relevant.

Insulin sensitivity is reduced in people on PIs and those on NRTIs, compared to those on no treatment. Disruption of insulin production can lead to the disruption of fat deposition, but no mechanism has been proposed to explain how HAART disrupts insulin production, except as a by-product of elevated triglycerides.

Impaired glucose tolerance may be present in people with HIV before starting treatment, although these results need to be treated with caution since they are derived from an African-American population in which an increased tendency towards impaired glucose tolerance might be expected in any case.

Other researchers believe that the syndrome is being unmasked by HAART, and that it is a result of long-term suppression of viral load. Although studies show a stronger association between body fat changes and protease inhibitors, the role of NNRTIs is not clear because few people have taken them for as long as PIs, and manufacturers have presented few data on this issue. Anecdotally, UK doctors have described patients with symptoms linked with this syndrome who are taking NNRTIs.

HEART DISEASE RISK

Dr Carl Grunfeld, an expert on lipids and HIV, told the Chicago conference that the pattern of lipid changes seen on HAART approaches the level at which clinical intervention for heart disease prevention would be recommended in the US.

However, using the Framingham guidelines for calculating heart disease risk (supplied to all US physicians), Dr Grunfeld has calculated that the average level of lipid changes being seen in patients on HAART would result in 1.41 new cases of heart disease per 100 patients over ten years, over and above any existing risk of heart disease. (HIV infection itself causes an increase in the risk of heart disease). However, these calculations do not take into account other risk factors such as above-normal blood pressure, smoking history, family history of heart disease and age (risk increases over 50). In men with all these risk factors, the risk increases to 27 new cases per 100 patients over ten years.

STOPPING PI TREATMENT

There is conflicting evidence about whether stopping PI treatment will improve body fat and metabolic changes. Although previous

conference reports have suggested that body fat can revert towards normal within a few months of stopping treatment, an analysis by Dr. Andrew Carr in Sydney found that fat loss in the limbs and face is not corrected within six months of ceasing PI treatment. The researchers suggested that fat recovery is either irreversible, or may take substantially longer than six months. These results are especially discouraging when viewed alongside improvements in blood fats and abdominal fat in the same patients, and suggest that separate mechanisms may be responsible for the various changes currently classified as 'lipodystrophy'.

Several groups reported on switching therapy. In the group discussed above, a switch to nelfinavir had no significant effect after three months. Amongst a small group of patients treated at a lipodystrophy clinic at the Chelsea and Westminster Hospital, a switch from a PI to efavirenz resulted in a significant increase in cholesterol levels after 12 weeks of treatment. These patients had experienced weight loss prior to the switch. On the new combination there was a significant weight gain.

Finally, two groups from Barcelona reported on the effects of replacing a PI with nevirapine in people with lipodystrophy. One group presented very early data from a randomised study in 21 patients and observed significant decreases in cholesterol and triglycerides after three months in nevirapine treated patients compared to those who remained on protease inhibitors. However, no significant improvements in body fat distribution were recorded.

Similarly, amongst a group of 23 people with undetectable viral load, a switch from a PI to nevirapine did not result in any significant improvement in body mass index or body fat distribution after six months, despite significant improvements in blood fat levels.

A concern in switching people who have undetectable viral load on a PI to an NNRTI is the possible loss of virological control. Each of the three studies above that switched patients in this way reported almost complete success in maintaining viral load suppression on the NNRTI-containing combination.

HUMAN GROWTH HORMONE

New York doctor Gabriel Torres reported on the use of human growth hormone to reduce 'buffalo hump' and abdominal fat. He treated thirteen patients, eleven of whom have experienced substantial reductions in fat accumulations. However, several people who stopped human growth hormone treatment experienced a return of fat deposits, suggesting that human growth hormone may need to be taken for an indefinite period and that it does not correct the underlying disorder which is causing these body fat changes.

NAM FORUM

The March Information Forum is an update on Opportunistic Infections, with guest speaker Professor Brian Gazzard. Venue: Palms Room, 4th Floor, University of London Union, Malet Street, London WC1. The date is Monday, March 29th, from 7pm to 9pm. This is a free event. All are welcome and a sign language interpreter will be present.

Treatment & pregnancy

New research on effectiveness and safety of combination therapy

BY ANNA POPPA

The effectiveness of AZT in preventing transmission of HIV from mother to baby was first reported in 1994. Despite subsequent advances which have caused transmission rates to fall as low as 1 in 50 in developed countries, the safety of combination therapy in pregnancy is unclear. New research presented at a recent conference in Chicago, and in the medical press, is reviewed here.

BETTER LATE THAN NEVER

The standard AZT course which is advised for use in the prevention of mother to baby transmission, often termed "the 076 regimen" after the study which established its efficacy, involves the mother beginning treatment in the second trimester of pregnancy, taking the drug intravenously during delivery, plus the use of AZT syrup in the infant for the first six weeks of life. There are several reasons for investigating whether shorter treatment courses may also offer benefit, for example:

- ◆ to limit the potential for side-effects in both mother and baby
- ◆ to establish more affordable interventions for use in the developing world, where the extent of perinatal transmission dwarves that seen in the western world
- ◆ because many HIV positive women do not have their infection diagnosed until late in pregnancy.

Early last year, a large trial in Thai women found that a short course of AZT begun around four weeks before delivery, without treatment for the infant, could lower the rate of mother to baby transmission by 50%. (The 076 regimen offers a two thirds reduction). Another study, of women in the New York area, was reported late last year in the *New England Journal of Medicine*. Looking at data on 939 infants born to HIV-positive mothers who did not breast feed, the transmission rate varied according to when AZT was begun. When begun in the prenatal period, the rate was 6%; 10% when begun during delivery; 9% when begun in the first 48 hours of life; 18% when begun on day 3 or later; and 27% with no AZT at all.

In Chicago, early results from two large trials investigating the use of short treatment courses in African women were presented. Both involved women who breast fed their children – recommended practice in many African countries in the absence of

alternatives, despite being a route of mother to baby HIV transmission. In the Ditrane Project (ANRS 049a) conducted in West Africa, women received AZT from weeks 36-38 of pregnancy until delivery, plus AZT during labour, plus AZT for 8 days after delivery (with no treatment to the infant); or an AZT placebo (until the Thai short course study was reported and the placebo arm was stopped).

The initial analysis involved 200 mother-infant pairs from the treated arm and 200 from the untreated arm. Caesarean sections were very uncommon but about 9 in 10 women breast fed. After six months follow-up of the infant, the transmission rate amongst treated mothers was 18% compared with 28% in the untreated group; a reduction in the risk of transmission of 38%. Given that the women who participated in this study are continuing to breast feed, whether this benefit may persist in the longer term is unclear.

The PETRA study is the first to investigate the use of a short course of AZT and 3TC. Women from South Africa, Uganda and Tanzania were randomised into four arms:

- ◆ AZT/3TC at 36 weeks, during delivery and in the infant for one week (Arm A)
- ◆ AZT/3TC during delivery and in the infant for one week (Arm B)
- ◆ AZT/3TC during delivery (Arm C)
- ◆ No treatment (Arm P). This arm was stopped following the Thai study.

In this trial caesarean section was more common, occurring in a third of women. Two thirds of mothers breast fed. After just six weeks follow-up, transmission rates for 1357 infants were: 9% Arm A; 11% Arm B; 18% Arm C; and 17% Arm P. Women and their children will continue to be followed. However, an immediate take-home message from PETRA which may perhaps be of relevance beyond the developing world, is the lack of difference in transmission rates between Arms C and P, suggesting there is no benefit in treatment during delivery alone.

NEWS ON AZT WITH 3TC

A study conducted in French women (ANRS 075) is the first to report on the use of AZT and 3TC in non-breast feeding women and proved to be one of the talking points of the Chicago conference. In this open study, mothers took the standard 076 AZT regimen with the addition of 3TC at the standard daily

CAESAREAN SECTION

Space prevents the role of mode of delivery in mother to baby transmission from being fully discussed here, and this will be the subject of a future article. See *AIDS Treatment Update* 68 for more information.

ADVISORY PANEL

We are pleased to welcome Dr Gareth Tudor-Williams to NAM's Medical Advisory Panel, a team of expert reviewers who comment on *AIDS Treatment Update's* content prior to publication. Gareth is Senior Lecturer in Paediatric Infectious Diseases at Imperial College School of Medicine, St Mary's Hospital, London.

dose from week 32 of pregnancy. Both drugs were given to the infant from birth to six weeks. Outcomes from the first 200 mother-infant pairs with more than six months follow-up of the child were compared historically with 899 pairs who had received AZT alone.

Overall, a 0.95 log reduction in maternal viral load was seen in those receiving AZT/3TC. The rate of transmission in the dual therapy group was 2.6%, compared to 6.5% in those receiving AZT alone.

There were no more premature deliveries, adverse events or significant differences in laboratory toxicities in women receiving AZT/3TC compared to AZT alone. However, the researchers reported that two children who had been exposed to AZT/3TC and who were uninfected, had presented at around four months of age and died around their first birthday from neurological (brain) disease. The experiences of both children have since been intensively studied. Both appear to have been affected by a mitochondrial myopathy which is known to be a possible side-effect of nucleoside analogue therapy.

Many obstetricians have experience of caring for HIV-positive women who have received AZT/3TC in pregnancy. This suggests that if these two cases were drug-related (which is *not* proven), then these are rare events. Nonetheless, mitochondrial dysfunction is extremely rare and the clustering of two cases within a sample of 200 infants has caused concern.

The American Centers for Disease Control plan to re-assess their registry of information on the use of antiretrovirals in pregnancy for any similar cases. In the meantime, current US guidelines advise the use of AZT monotherapy in pregnancy unless the mother's own disease status suggests that this is inadequate treatment for her.

AZT remains the only antiretroviral which has been thoroughly studied in pregnancy, and for which medium-term follow-up on exposed mothers and infants is available. In a recent issue of the *Journal of the American Medical Association*, researchers reported four year follow-up on 234 uninfected children born to HIV-positive women who took the 076 regimen in pregnancy. There was no evidence of a significant difference between these children and untreated children in terms of clinical signs or development.

SAFETY OF HAART IN PREGNANCY

A small study presented at the Geneva World AIDS Conference suggested a possible connection between the use of protease inhibitors (PIs) in pregnancy and premature delivery. Subsequent research has not supported this finding, suggesting instead that

prematurity is associated with HIV disease and is probably not drug-related. This was further supported by two new studies presented at the Chicago conference. The first reviewed medical records of 89 women taking PIs in pregnancy, 76 of whom gave birth. 30 were on treatment at conception or in the first trimester and 40 began in the second. There were no differences in proportions receiving either nelfinavir, indinavir or saquinavir, though only five received ritonavir. There was no additional risk of prematurity amongst these women than among comparable women treated at the same centre without PIs. Infant follow-up was short however, with 55 of 76 followed less than two months.

In a similar review of 73 women, 53 of whom delivered, HAART was not found to be associated with additional adverse events. In this study, women had received NRTIs with nevirapine or PIs, or with both.

RITONAVIR IN PREGNANCY

Researchers from Thailand were the first to report on the effects of a short course of ritonavir, begun in the 36th week of pregnancy in 86 HIV-positive, treatment naïve women who did not breast feed. Ritonavir was taken for 19 days on average and was associated with an average fall in viral load of 1.5 logs.

The rate of transmission in 74 women who remained on treatment was 9.5%. 12 women stopped their treatment, (10 due to elevated liver enzymes; 1 severe vomiting, diarrhoea, headache and fever; 1 inability to take the capsule). The most frequently reported maternal adverse events included diarrhoea (30), nausea (22), changes in taste (15) and vomiting (10). There were 51 maternal grade 3/4 laboratory abnormalities (mostly elevated liver enzymes) and 24 in infants.

A second, much smaller study also suggested that use of ritonavir in pregnancy may be associated with significant side-effects. 6 women took part in a phase I study of ritonavir/AZT/3TC (PACTG 354). One woman had an early caesarean section at 31 weeks due to oligohydramnios (little amniotic fluid around the baby) and decreased fetal heart sounds. This baby subsequently died of a bacterial infection aged 11 days. There were two more premature births and both these infants had grade 4 hypoglycaemia (low blood sugar), which resolved with glucose treatment. Four further grade 3/4 adverse events were reported in the infants.

Treatment appeared to be well tolerated by the mothers and there were no discontinuations. This very small sample, and the lack of comparison cases, makes it difficult to assess the significance of these outcomes, though further follow-up is clearly warranted.

TRANSMISSION OF MULTI-DRUG RESISTANCE

The first report of mother to baby transmission of multi-drug resistant HIV (resistant to both PIs and NRTIs) was amongst several sombre presentations on perinatal transmission in Chicago. It occurred in the case of a mother with a long treatment history including mono and sequential therapies, not untypical in the US.

Given the high incidence of drug resistance which was the subject of other reports at the conference, several delegates were left considering a future role for resistance testing in pregnancy.

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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

cytotoxic Cell-killing

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

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

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

mitochondria Cellular factor involved in energy production

myopathy Progressive muscle weakness

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

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 nucleotide analogue A type of reverse transcriptase inhibitor

placebo A dummy pill used in trials

primary infection Time immediately following infection with HIV

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

recombinant resistance Genetically reconstructed 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

seroconversion Time at which antibody status changes from negative to positive

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

viraemia The presence of virus in the blood

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

Subscriptions

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

Medical Advisory Panel

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

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

◆ Body Positive

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

◆ The Terrence Higgins Trust

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

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

The publishers have taken all such care as they consider reasonable in preparing this newsletter. But they will not be held responsible for any inaccuracies or mis-statements of fact contained herein. Inclusion in this newsletter of information on any drug or clinical trial in no way represents an endorsement of that drug or trial. This newsletter should always be used in conjunction with professional medical advice.

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