



The Birchgrove

THE BIRCHGROVE GROUP, P.O. BOX 9, ABERTILLERY, WALES NP13 1YD. TEL: 01222 520045

Knowing when to stop.

New research prompts warning to people on treatment:

Don't try this at home

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 RIGHi; 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 nucleoside 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 1 6,000 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 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

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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 anti-retroviral 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.

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)

QUEST STUDY

This study is designed to assess if treatment (with Combivir, abacavir and zidovudine) 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

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on three drugs versus four after an initial four drug induction period. Trial sites are in Belfast, Brighton, London and Manchester. Absorption for Efavirenz is around 15 hours, nevirapine around 30. 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/ zidovudine and had a constant metallic taste in my mouth. I decided that I wanted to taste my Christmas dinner, so I stopped taking zidovudine. 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 zidovudine 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 other HIV specialist services 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.

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WHATS NEW

Immune therapies are treatments which influence or modify certain components of the immune system. Apart from drugs designed to attack HIV directly, a number of immune therapies are also being investigated for use by people with HIV for the purpose of boosting immunity and to try to correct the abnormalities seen in HIV infection.

Interleukin-2 (IL-2)

Cytokines are chemical messengers secreted by immune cells which co-ordinate and control the intricate workings of the immune system. IL-2 is a type of cytokine which encourages the growth of CD4 T-cells. Genetically engineered, or recombinant, IL-2 is being tested as an immune therapy for people with HIV

IL-2 is a very efficient trigger of HIV replication, because when it activates CD4 cells it also activates HIV-infected CD4 cells. For this reason, IL-2 has tended to be tested in combination with anti-HIV therapy to suppress the HIV activation.

A current UK study is investigating its use alone. Other research is looking at whether IL-2 might have a role in attempts to purge HIV from the reservoirs of long-living immune cells which appear to be persistently infected despite long periods of potent anti-HIV therapy.

People treated with IL-2 plus anti-HIV therapy experience a significant, sustained improvement in their CD4 counts compared to people who receive anti-HIV therapy alone. It is not clear whether this signifies improvement in the function of these CD4 cells. It's also not clear at present whether IL-2 will affect the long-term risk of disease and death.

Today, IL-2 tends to be given in five day cycles which recur every couple of months. Treatment is given by subcutaneous (under the skin) injection to improve the rate of side-effects. However, side-effects can still be very unpleasant, often described as similar to a bout of flu.

Remune

A vaccine is a substance intended to stimulate the body's own immune defences against a micro-organism. While preventative vaccines are designed to protect the recipient against initial infection with a micro-organism, therapeutic vaccines are designed for people who are already infected with a micro-organism.

In HIV research, the lead candidate in this category is Remune, a therapeutic vaccine made from HIV particles which have been made harmless. The theory is that by injecting these particles into people who are already infected with HIV the immune system may be stimulated to mount a greater response not only to the killed HIV particles in Remune, but also to real virus particles and HIV-infected cells in the body.

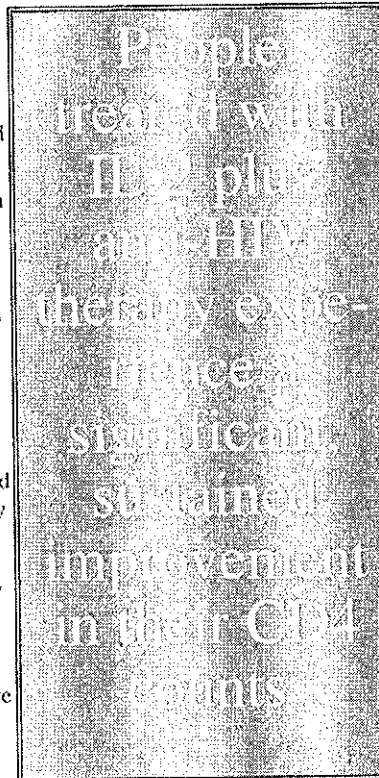
Current trials suggest that, in the test tube, Remune increases CD4 cell response to HIV to a higher level even than that seen in long-term non progressors, at least over the relatively short period studied so far. It is unclear if this will translate into a benefit in terms of protection against illness and death over the longer term, and this is the subject of several ongoing trials. Other than infections around the injection site, side-effects from Remune have not been reported.

Immune restoration with anti-HIV drugs

At present, the most commonly used immune boosting therapy is anti-HIV treatment itself. Most people who respond well to combination therapy have a dramatic increase in their CD4 count in the first few months of treatment, followed by a more gradual rise during subsequent months.

This later phase is accompanied by improved function and restoration of a wider range of immune responses.

Until relatively recently, there was concern that immune recovery may not be possible for people whose immune damage had reached a 'point of no return'. However, there are now many studies showing that even people with extremely low CD4 counts can experience very substantial increases in their CD4 cells during combination therapy. This recovery of immune capacity is responsible for the declining disease and death rates seen amongst people with HIV in much of the developed world.



NAM also publishes a free monthly newsletter, **AIDS Treatment Update For details ~ of this and our other HIV treatment publications, phone 0171 627 3200 or write to NAM Publications, FRFEPOST LON277, London SW4 7YY. <http://www.aidsmap>**

Relationships

P.O.Box Private

I advertised for a relationship at the end of last year. It began with encouragement from my community haemophilia nurse that perhaps now was the time to start looking for a new relationship. Egged on by friends of mine I composed an advert with them and then after a few more bottles of wine one of them rang up the phone line. My friend then presented the phone to me and a voice demanded my name and address and drunken message. Fortunately I received a letter in the post a few days later that explained when my message would appear in the paper and how I could re-record the message. I started writing a new one and then recorded a sober version of the message.

Early thirties, living in Brighton, likes food, drink and European cities; hates Barbara Cartland novels, horse racing on TV and Country and Western music; I speak English German and after a few pints, crap. I want to meet an intelligent woman who will tell me to shut up when I start talking rubbish.

The advert was to be printed three weeks later which sadly was the start of a week's holiday for me. So everyone who left a message had to wait a week before I replied. The ad was quite successful with 17 women leaving messages - it took half an hour just to listen to them all. I also had writers cramp after taking the details of each one down. I managed to speak to twelve of them on the phone with the rest being unobtainable or sounding dull.

From the twelve I met six and one either did not show up or was lost in the crowd that suddenly appeared where we had arranged to meet. There was no reply each time I rang her afterwards. It took over a month to see all of them as I had another trip out of the country planned and everyone was getting flu. Some were nice but dull, one was really fun and one was really stunning. This latter one said her friend wanted a medical report on any possible lovers because she kept going with out disabled people and ending up looking after them.

From the six, I saw three a second time. One then did not ring me or answer messages after the second date and I was left with two; T.... and M.... With the number down to a manageable level I could also throw away the notes I had kept to ensure I did not call anyone by the wrong name or ask about the wrong job. By now I had friends across half of Europe wanting information about these women along with my original friends and the community nurse. And all of them asking the same questions - Have you snogged any of them? When will you sleep with one of them?

I spoke to both of them quite a lot on the phone but decided I should talk about my status face to face. I told T.... that I had haemophilia and HCV the second time I met her which was not particularly easy. Especially as she was the one who'd said she did not want to end up looking after someone again. I planned to do it half way through the evening so that there was plenty of time for me to explain afterwards but it was not the first thing I said. It seemed to go fairly well or as well as these things can go. She rang me later and asked how

could I say these things ten minutes before she had to go which I suppose shows how time flies when you're having fun. It felt like a very long hour to me but when I asked if I could see her again she agreed.

Christmas then intervened, as it does at the end of every year and I decided not to tell M.... my status until she returned from her parents. I then got a stomach bug, (why is it when ever I tell someone I have HIV I always get flu or a stomach bug within the next fortnight and scare the hell out of them), T.... looked in on me after work a few times which was very nice. One particular evening though, after she had been at my house for about an hour, she got up abruptly and left. I was not sure what I had said but felt I had probably fucked it up somehow. Then she rang me from her mobile and said that she felt she had to go because otherwise she would have wanted to make love to me.

Then we were cut off as mobiles always do at crucial moments. However after much flattery and begging she agreed to come back to my house. This ensured I did at least have a traditional Christmas, all morning cooking a turkey, all afternoon drinking and half the evening having drunken sex. It was a great day. She dumped me on Boxing Day.

We saw each other on Boxing Day and had a very adult type discussion about what had happened. She felt she could not handle a relationship with someone who was positive and the inevitable stress it would cause for her and her family. After a long talk she changed her mind and decided she could go out with me. I naturally instantly changed my mind and decided that I did not want to go out with her now. She then left messages for me on my answerphone and I rang her the next day. I stuck to my line of not going out with her, she was not impressed. In the meantime M...., having said she would call me after returning from Birmingham had not. I Left a message but still nothing. T.... and I decided to try and be friends and went out a couple of times to the cinema and for a drink which seemed to go very well. And on the third time I saw her we slept together again. The next day M.... rang.

She had been ill with flu quite badly and stayed an extra week at her parents. We chatted and I promised to ring her in a week when she would hopefully have recovered. T.... and I continued to get on better and we even decided to go for a weekend away. The problem with living in Brighton though is where the hell do you go for a dirty weekend. We decided on the short lighthouse on the coast between Carliff and Newport.

I rang M.... of course and decided to tell her the next time I saw her that I was now with someone. She however beat me to it. I was not the only advert she had answered and was now seeing someone else through the paper called Matthew.

Could we have a part two, or an update please? (Ed)