ISSUE FOURTEEN

Keep taking the pills

The Birchgrove

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Bath Success

A brief report

NATIONAL BIRCHGROVE CONFERENCE REPORT
BATH 24TH - 26TH JULY 1998
INTRODUCTION

The 5th National Birchgrove Conference was held at the Stakis Hotel, Bath, over the weekend of 24th - 26th July 1998, on the theme of "Treatments and Alternatives". The intention of the conference organisers was to provide a forum for discussion of conventional combination therapies and complementary treatments for haemophiliacs co-infected with HIV and Hepatitis C.

Friday 24th July

REGISTRATION AND WELCOME

Delegates from all over the country began to arrive at the Stakis early on Friday afternoon. Registration was completed by 7.00 pm with a total of 60 delegates in attendance. Rather than scheduling seminars for Friday evening, this time was set aside for old acquaintances to be renewed and for first time attendees to meet with and get to know the old hands. A three course dinner was arranged for 8.00 pm in the Willow Suite, where a fine meal was accompanied by some lively discussion on the business of the conference.

Afterwards, people retired to the main bar where the talk continued into the early hours. The atmosphere throughout the evening was relaxed and convivial, and there appeared to be a note of cautious optimism about the future.

Saturday 25th July

HIV/HEPATITIS C CO-INFECTION

Following a hearty breakfast, delegates decamped to the Willow Suite for the first Seminar. Cady Khudabux, on behalf of the National Birchgrove Steering Committee, welcomed the delegates to Bath and introduced them to other members of the organising committee. He outlined the agenda for the weekend and then introduced the first speaker, Nigel Hughes, the Clinical Nurse Specialist at Preston Hall Hospital, Maidstone in Kent. Nigel gave a lively and informative talk on HIV and Hepatitis C co-infection, speaking for approximately 45 minutes on a number of issues relating to this topic, including current treatments with alpha-interferon, and also the long-term prognosis for those who were co-infected. Subsequently, questions were invited from the floor and the number of people wishing to put questions to Nigel was indicative of the high level of interest his talk had generated.

MACFARLANE TRUST OPEN FORUM

After a break for tea and coffee, there was an Open Forum with three representatives from the Macfarlane Trust describing the workings of the Trust and their roles and responsibilities within the organisation. Tim Hunt, Fran Dix and Anne Hithersay gave delegates a valuable insight into the Trust's policies and procedures on a number of issues, ranging from how decisions are made regarding grant awards, to the criteria needed to apply for such grants. Enthusiastic delegates raised a number of pertinent questions on past decisions and on the future direction of the Trust.

CHILDREN'S TRIP TO BRISTOL ZOO

The Birchgrove Children and Families worker, Martha Cirino, with the help of volunteer Choy Sterio, had organised a children's day out at Bristol Zoo. A total of seven children were taken by train to Bristol in the morning, thus allowing their parents to attend the day's seminars. All the kids were returned safe and sound to the Stakis at around 4.30 on the Saturday evening.

ATP: COMBINATION THERAPIES

After the morning's sessions, lunch was served between 1.00 and 2.00 pm, with delegates returning to the Willow Suite for the main business of the afternoon, a question and answer session on the latest

continued on page 2

continued from front page

news regarding Combination Therapies. This talk was conducted by Rafi of the AIDS Treatment Project and provided a platform for delegates to voice their fears and concerns regarding a wide variety of treatment issues. With different levels of knowledge emanating from the delegates, Rafi managed to conduct the discussion at a level which seemed to offer something to everyone. Issues raised included when was the best time to begin treatment; what was meant by CD4 counts, viral load tests and HAART; the consequences of delaying treatment; the different classes of drugs, i.e., nucleoside analogue reverse transcriptase inhibitors (NRTIs), such as AZT, DDI, 3TC and D4T, non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), such as Nevirapine, Delaviridine and DMP 266, and protease inhibitors (PIs) such as Ritonavir, Indinavir and Saquinavir. Other issues discussed related to drug side-effects, and when and if it would be possible to cease drug treatment.

Rafi also gave delegates up to the minute feedback on developments at the recently held World AIDS Conference in Geneva. While some of the news was relatively depressing – for example on the serious side-effects connected with long term treatment on Protease Inhibitors, other news struck a more cautiously optimistic note. Doctors and AIDS specialists were developing what had been termed 'Protease Sparing Regimes' for treating HIV infection, and there was talk of new NRTIs being available in the near future, as well as the development of a whole new class of anti-HIV drugs.

The seminar ran for over two hours, with a coffee break in between, and while there was a lot of information to take on board, much of it new to many delegates, it proved to be an interesting and informative session.

MEAL AND DISCO

In the evening, another three course dinner was followed by a disco in the Willow Suite. This provided ample opportunity for various delegates and steering committee members to make spectacles of themselves either on the dance floor, or through their truly appalling taste in music. The disaster of the Haemophilia Society's soon to be wed HIV worker ending up having a midnight dip in the Stakis lake, courtesy of a number of female delegates, was narrowly averted by the judicious – and as yet unrewarded – intervention of two members of the steering committee. That he didn't get ducked perhaps indicates the high esteem in which he is held. Or maybe not, as the case may be.

Sunday 26th July

TRADITIONAL CHINESE MEDICINE

Unfortunately, the representative from John Tindall's Gateway Clinic in London, scheduled to give a talk on Traditional Chinese Medicine, did not turn up. Instead, Mike O'Driscoll gave a talk on the subject from a patient's point of view. Mike had been using Chinese Herbs for two years in the treatment of both his HIV and Hepatitis C infections. He explained how the initial consultation with John Tindall was designed to enable the practitioner to gain an overall picture of the patient's health and well-being, with particular attention being paid to specific indicators – pulse, respiration, tongue, mental and emotional health, etc. A prescription was then drawn up by the practitioner, which could include up to twenty or thirty different Chinese Herbs in various quantities. Whilst the consultation with John Tindall is free of charge, the patient has to pay for the herbs, which, according to the prescription, can vary in cost up to £35.00 for a months supply.

Treatment consists of boiling a quantity of herbs in a litre of water, straining and reserving this mixture and then repeating the process. The resultant liquid was enough for four days treatment, which consisted of approximately half a cup drunk twice a day. The liquid could be drunk hot or cold, but Mike advised that it was best to drink it down in one quick gulp, and have something more palatable at hand to get rid of the unpleasant aftertaste. Mike talked for about twenty minutes and then answered questions from delegates. From a personal point of view, he told the conference that he felt the herbs had had a beneficial effect on his health, and that it was a shame that a representative from the clinic had not turned up, as they did have statistical evidence to show such benefits to health.

HAEMOPHILIA SOCIETY'S HIV WORKER

Steve Fouch held a question and answer session during the second half of the morning. Steve, the Society's HIV worker, explained his role within the society and how it related to the Birchgrove Group. He is closely involved in projects with both National Birchgrove and Birchgrove Wales, and sees part of his role as developing links with local Birchgrove groups in other parts of the country – the North-west, north-east, East Anglia and the Midlands, for example. He also intends to encourage other HIV+ haemophiliacs that he may come into contact with, and who have not previously had any links with Birchgrove, to get in contact with the group.

Again, this was an interesting and informative session with lots of questions from the floor. Given that this was largely an impromptu session, due to the non-appearance of the Chinese Herb specialist, delegates felt that it was worthwhile in that it gave people a chance to meet Steve and gain an understanding of his role.

Sunday Lunch was served between 12.30 and 2.00 pm, after which the conference drew to a close, with delegates returning to all corners of the country.

KEEP TAKING THE PILLS

RESISTANCE

After a person is infected with HIV, many different strains of the virus appear over time as the virus copies itself. Each new generation has tiny differences, or mutations, in its structure. Some of these mutations occur in the parts of HIV which are targeted by anti-HIV drugs. This can result in strains of HIV that are less vulnerable to treatment.

When an anti-HIV drug is started, HIV strains that are highly vulnerable to the drug disappear rapidly. This leaves strains behind that can copy themselves despite the drug's presence. In time, the 'pool' of viruses will include fewer and fewer drug-sensitive strains and more and more resistant ones. These may or may not be capable of harming the body.

Resistance is an important reason why many anti-HIV drugs have only limited or short-term effects. Whenever HIV is still able to reproduce in the body of someone who is taking anti-HIV drugs, it is extremely likely that resistant strains will eventually emerge, and the viral load will increase. This increase is sometimes called viral load 'rebound'.

MINIMISING THE RISK OF RESISTANCE

Using two or more anti-HIV drugs at once, known as combination therapy, delays resistance, because viruses that are resistant to one of the drugs may still be controlled by the other(s).

Studies have shown that the risk of viral load rebound is related to the point to which viral load falls after starting treatment, called the 'nadir'. The lower the nadir, the lower the risk of rebound, and therefore the risk of resistance.

People whose viral load falls, and remains, below 50 copies are at a much lower risk of developing resistance. However, resistance may emerge even in these people over the longer term. (Most viral load tests currently in use in the UK measure viral load to a lower limit of 400 or 500 copies. Ask your doctor about the tests available in your clinic).

Adding or changing a single new drug to a combination which is not suppressing viral load is likely to lead to the development of drug resistance, because the impact of that single new drug is likely to be insufficient to block replication. Experts now advise that treatment changes should always include at least two new drugs, wherever possible.

Continuing with the same drugs after your viral load begins to go up can also encourage the development of resistance. This is because resistance to some drugs develops progressively; as more resistant mutations accumulate, sensitivity to the drug will fall. However, resistance to drugs emerges at different speeds. For example, 3TC and nevirapine resistance emerges very quickly, but d4T and ddC resistance emerges slowly.

Also, people whose viral load remains high or rebounds whilst taking anti-HIV drugs may still experience a rise in CD4 count, and delayed disease progression. Though resistance is a common reason for viral load rebound, it is not the only reason.

It is important to take anti-HIV drugs exactly as they have been prescribed, by sticking rigidly to the suggested dose and timetable, and observing instructions about food.

Taking too little drug (by missing or reducing doses) could allow drug levels in the blood to fall to inadequate levels, allowing viral replication to occur and increasing the risk of the emergence of resistance.

CROSS-RESISTANCE

Single mutations, or sets of mutations, in the virus can produce resistance to several different drugs. This means that once resistance to one drug has emerged, this virus population may also be resistant to drugs you haven't taken yet.

This is called cross-resistance and may affect all currently available anti-HIV drugs to a greater or lesser extent. For example, it is possible that if you develop resistance to a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI), you will also be resistant to all others in the same group.

RESISTANCE TESTING

Several tests are being developed to detect which drugs you are resistant to and your level of resistance to them. It is not currently known how useful these tests will be in guiding treatment decisions.

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HAART

Two Three or Maybe FOUR BY DR STEPHEN ASH

One reads reports of clinical trials of new drugs and combination therapy and how good they are at producing quite dramatic drops in viral load (expressed as multiple log falls*) and rises in CD4 counts. But how well are things going in the real world outside of clinical trials?

Certainly there are reports of hospital wards closing due to reductions in the numbers of opportunistic infections in people who have responded to HAART (highly active antiretroviral therapy). On the down-side we have heard about problems with HAART, for example drug failure due to viral resistance, and side-effects such as lipodystrophy – abnormal distribution of fat in the body.

It is more than two years since patients at Ealing Hospital were first offered HAART (which in practice has usually meant triple combination therapy including a protease inhibitor) and it seems like a good idea to take stock of the situation and see what can be learnt. Although the following data is very preliminary, it gives a rough idea of trends and responses to HAART we have encountered.

Over 50 patients are on triple or quadruple therapy at Ealing Hospital, in most cases including at least one protease inhibitor. The majority of these patients are gay males as we would expect from the pattern of infection.

However, over forty per cent are heterosexual and almost twenty five per cent are women.

More than eighty per cent of those starting HAART achieved an undetectable viral load (less than 200 copies/ml) within four months. Most of the twenty per cent who didn't achieve this goal hadn't taken the drugs regularly as advised. However, about half of all patients on HAART had to change their therapy in the first year. About one third changed a single drug due to side effects, although their viral load was less than 200.

The remaining two thirds had to change two or more drugs on the basis of rising viral load. Poor compliance accounted for many of these instances, but not all. Those people with previous experience of taking antiretroviral drugs tended to be more likely to develop drug failure.

Despite all the problems of HAART, it has been a privilege to witness the amazing benefits that some patients have clearly received from these drugs. The hospital admission rate has dropped as a result of a fall in the number of opportunistic infections and other serious infections that one would have expected to see. Although this parallels the rise in CD4 count seen in most patients, even those patients with only a modest rise in CD4 count seem to get some form of protection against infections.

All this has resulted in an increased life-expectancy for people on HAART. The rate of CMV and MAI infection has fallen by ninety per cent; that of Cryptosporidium and Pneumocystis pneumonia by one hundred per cent (no new cases). The incidence of Candida seems to have been reduced by a more modest seventy per cent. We have witnessed the regression of Kaposi's sarcoma upon commencement of HAART, as well as some improvements in PML and HIV encephalopathy. However, there has been no improvement in the incidence of HIV-related tumours such as lymphomas.

As has been reported by other centres, the enhanced immune system response that follows HAART can be temporarily harmful. We have seen one patient with a flare-up of their CMV retinitis although this did settle fairly quickly with prompt treatment.

Additionally there have been several patients who started HAART with very low CD4 counts whose previously undiagnosed MAI of the lymph glands became obvious once the immune system became strong enough to attack the infection. This resulted in swelling and discharge from the lymph glands. Once again the eventual outcome was good thanks to rapid diagnosis and early treatment.

As time goes by, we are more and more aware of the longer term problems of HAART and we routinely monitor for all sort of complications such as:

- *High blood sugar levels*
- *High cholesterol and triglyceride (fat) levels*
- *High blood pressure*
- *Lipodystrophy*
  (abnormal fat distribution)
- *Osteoporosis*
- *Kidney stones*
  (associated with indinavir in particular)

Early warnings and intervention can minimise the impact of such problems.

Despite much emphasis on side-effects and worries about as yet unrecognised long-term problems with the use of many of the new drugs that make up a HAART combination, it is nevertheless clear that most people who start HAART receive enormous benefit and it appears that for most people this is an effect that can last for years.

Dr Stephen Ash is Consultant Physician in General Medicine and Infectious Diseases at the Ealing Hospital NHS Trust.

***Multiple Log Falls (of viral copies)**

From 1,000 to 100 = 1 log fall (10^3 to 10^2)

or

From 10,000 to 10 = 3 log fall (10^4 to 10)

Letters Page

Dear Manor House group

I'm the partner of a dual infected haemophiliac. I have wanted to access your group for a while now but I have heard of evidence that dual infected men and their families are not welcomed within your group. This seems ludicrous to me as, is it not the fact that all these boys and men share common factors, they all have haemophilia. They were all infected with one or all of the following diseases; hep B, hep C, HIV, through contaminated blood products.

Should it not be possible for the Manor House group to work and learn from members of such groups as the Birchgrove group and the Macfarlane trust. After all we are struggling with hep C, issues as well. I feel unhappy with the knowledge that the haemophilia community is divided in this way.

Yes we have our "recompense" (*ed*) for HIV/AIDS, but out of 1200 infected there are only 480 still living. Surely 480 extra voices to the cause of compensation is better than no extra voices at all. Obviously we don't know if all the remaining men are hep C positive, as patients records are out of bounds to other haemophiliacs.

I have also discovered that there are no up to date national statistics at present relating to haemophiliacs with any of the afore mentioned diseases.

I would like to know how many men have never taken any treatments for HIV or HEP C? I would like to know how many men are not responding to treatments like interferon and combination therapies? What symptoms are they experiencing? We as loved ones have a right to know these statistics! How many haemophiliacs are there alive infected with HEP C?

If every centre director in the UK allowed the Haemophilia Society to collate this valuable information, then we as a community would have some solid evidence to show the government exactly how many lives have been destroyed.

You would then have solid evidence of exact numbers of HEP C positive haemophiliacs. Also please note that dual infected men are at greater risk of liver disease or full blown AIDS/death. HEP C therefore speeds up the degeneration of the immune system.

Another point I would like to make is that my partner and I were very disappointed with the news coverage and press conference relating to the lobbying of parliament. Using speculative figures, 90% of men infected with HIV were already infected with HEP C. There was no mention of the men who have both diseases.

You have let my family and countless others down by not stressing this point to the media and parliament.

I'm sorry that you didn't get the result that you wanted but ask the Birchgrove group and the Haemophilia Society for help and maybe we can win the battle next time. Thank you for reading my thoughts and I hope this may stir all your families to unite with us isolated and still very angry old hats!

Awaiting your responses,

Claire Moirano.

Spontaneous Bleeding

Protease Complications

What are the specific issues facing people with haemophilia and hepatitis? Recently, AIDS Treatment Update has received several calls from HIV-positive people with haemophilia, over reports that protease inhibitors may not be safe for them to take.

The concerns stem from a letter sent by the US Food and Drug Administration (FDA) to American doctors on 1 July 1996. It reported 15 cases of spontaneous bleeding episodes among people with haemophilia in Europe who were being treated with saquinavir, indinovir or ritonavir at the time. Since then, a substantial number of cases of unusual bleeding have been reported world-wide among haemophiliacs receiving protease inhibitor therapy.

Most of the bleeds have been of a type known as haematomas, in which the bleeding occurs into body tissues, causing a swelling. Only a minority of these bleeds have been haemarthroses (bleeding into a joint), the type that is most common among people with haemophilia.

CAUSE OR COINCIDENCE?

The FDA stressed that there is no conclusive evidence that these unexpected bleeds were caused by the protease inhibitors (PIs). It is possible that it was simply a coincidence that these people were taking a PIs.

There were no reports of increases in bleeding or blood cloning problems among haemophiliac or non-haemophiliac participants in clinical trials of protease inhibitors. In a study reported at the annual Retroviruses conference in Washington in Spring 1997, French researchers reported that two out of 21 non-haemophiliac people showed signs of blood cloning abnormalities after they started treatment with ritonavir or indinavir (abstract 201).

ANECDOTAL EVIDENCE

Dr Keeling, a consultant at the Haemophilia Centre at Oxford's Churchill Hospital, agrees that "the evidence is really anecdotal. If there is a real link with protease inhibitor treatment, we don't know whether it's something that will only affect a small minority of patients, or whether everyone is at an increased risk of bleeds. No-one has come up with any explanation of how the protease inhibitors might cause an increase in bleeding. I still remain slightly sceptical."

Dr Keeling expressed concern that the reports might be used as a pretext to prevent giving Protease Inhibitor Therapy to people with haemophilia. "If a person with haemophilia needs treatment with a protease inhibitor they should receive it, and be monitored carefully. These reports shouldn't be used just as an excuse not to give expensive drugs to people with haemophilia."

Nevertheless, there continue to be reports of bleeding problems apparently related to protease inhibitors. At the recent Hamburg Conference, Spanish doctors reported that 5 out of 17 haemophiliacs who were treated with indinavir as part of their combination therapy developed bleeding episodes; the three major bleeds were all haematomas.

YET MORE ANECDOTAL EVIDENCE

The evidence has increased for unusual bleeding amongst the haemophilia/HIV population. Anecdotally and fortunately, this unusual spontaneous bleeding has shown to decrease, after the compliant use of protease inhibitors over a period of five to six months.

Irish doctors also reported on their experience of treating 20 haemophiliacs with PIs. While there was no statistically significant increase in the number of bleeding episodes or in patients' requirements for the Factor VIII used to treat and prevent bleeds, two individuals with severe haemophilia did report unusual haematomas.

While the some of people with haemophilia and HIV have not experienced problems with protease inhibitors, the uncertainty has left many either very cautious about or already decided against taking a protease inhibitor.

RECENT STUDIES

Unfortunately recent studies suggest an intolerance of HIV protease inhibitors in HIV/HCV+ individuals receiving Highly Active Anti-Retroviral Therapy (HAART). Liver toxic reactions were more common in HIV/HCV+ individuals receiving the protease inhibitor – Indinavir (Crixivan), though they remain a minority of individuals. Chronic HCV is an independent pointer of liver toxicity and is found more in individuals with HIV/ HCV+ via people with haemophilia or injecting drug use.

While other protease inhibitors were apparently indicated less in this side effect, full and larger studies to evaluate the problem are needed. There is no evidence as yet that 'protease sparing regimes' using nucleoside (NRTIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs) cause similar difficulties, with few reported antagonistic effects between these therapies and Alpha Interferon therapy for chronic Hepatitis C.

Certainly HIV+ individuals co-infected with HCV need to be monitored for side effects and interactions between the differing therapeutic agents used for both viral infections.

GENERAL SYMPTOMS AND THEIR DIAGNOSIS

HIV infection and AIDS are associated with an increased incidence of a large number of symptoms, such as fatigue, dry skin and intermittent diarrhoea. These symptoms are seen with many illnesses. It is not within the scope of this article to deal with these individually, but it is possible to discuss in general some of the more common symptoms.

Swollen glands (lymphadenopathy) may be present in the groin, armpits and neck, and these are often tender. Some doctors believe it to be a good sign of the body responding to the HIV infection. The swollen glands are usually generalised and fluctuate in size, but sometimes one particular gland enlarges much more than others. Your doctor may wish to remove or sample (biopsy) such a gland to exclude infection or cancer.

Diarrhoea is a common symptom which may lead to weight loss and wasting. If it is persistent your doctor will ask for samples of your stools. There are many causes for diarrhoea including anxiety, common bowel infections (e.g. giardia, rotavirus, campylobacter, salmonella), and AIDS related opportunistic infections such as cryptosporidium and microsporidium.

These infections may be passed by contaminated food and water so it is important to listen for health warnings about food and water. Some people recommend boiling all drinking water. These infections may also be passed on by some sexual practices. Your doctor will be able to suggest specific treatment for diarrhoea, but it is essential to maintain your nutrition and fluid intake during a bout of diarrhoea.

Fevers and night sweats may occur due to HIV infection itself or an underlying infection. Some people need to change bed clothes because of sweating. Aspirin and paracetamol will often cause sweating when given for a fever, as this is part of the body's normal cooling system. Your doctor may wish to take blood cultures or other tests if you are having frequent night sweats.

Easy bruising and bleeding may occur if the 'platelet' count falls due to HIV. This is called thrombocytopenia and occurs in many circumstances other than HIV. There are a variety of treatments for this but in the first instance your doctor will probably suggest antiretroviral treatment.

SEROCONVERSION ILLNESS

Seroconversion illness is a viral syndrome that usually occurs within one month of being infected with HIV. It causes symptoms similar to the flu, such as sore throat, swollen glands, fevers, and aches and pains. Many people have fatigue and a rash similar to that seen in glandular fever. In up to 20% of people the symptoms are serious enough to consult a doctor, but the diagnosis is frequently missed. Even if an HIV antibody test is done at this time, it may not yet be positive. Some people consider that treatment at the time of seroconversion may have long term benefits by altering the viral load set point (level). If HIV infection is strongly suspected, your doctor may employ other tests (e.g., PCR) to confirm the diagnosis.

ANTIRETROVIRALS

There are currently two classes of drug licensed to directly treat HIV infection (antiretrovirals). These are nucleoside analogues and protease inhibitors. Another class becoming more widely used are the non-nucleoside reverse transcriptase inhibitors (NNRTIs), these are not yet licensed and are available through specialist HIV centres and clinics.

Deciding when treatment should be started, and which drugs should be used, is very much an individual decision which will need to take into account such factors as a person's viral load and T4 count.

It is vitally important that once started, medication should be taken at regular intervals, with the appropriate diet (i.e. fasting or after meals) and without missing doses. Clear instructions should be provided by your doctor or another health professional.

If drugs are not taken correctly, (i.e. there is not full compliance), then the drugs may soon become ineffective as the virus becomes resistant. Due to the phenomenon of 'cross resistance' this may mean not just one but a number of drugs become ineffective against HIV.

The BHIVA guidelines suggest a minimum of three drugs in combination to treat HIV ("combination therapy"); so increasingly, two drug combinations are used less. Single drug treatment (monotherapy) soon fails and should never be used. There is no single "correct" combination of drugs which should be taken.

NUCLEOSIDE ANALOGUES

Nucleoside analogues work by inhibiting a specific HIV enzyme called reverse transcriptase, and the following nucleoside analogue drugs have been licensed in the UK: zidovudine (AZT, Retrovir), ddI (didanosine, Videx), ddC (zalcitabine, HIVID), 3TC (lamivudine, Epivir) and d4T (stavudine, Zerit).

ZIDOVUDINE (AZT, Retrovir)

Zidovudine was first licensed for use in the treatment of HIV infection in 1987, when a trial showed that people who took zidovudine lived longer than those given a placebo (inactive tablets). It also showed that the zidovudine recipients developed fewer opportunistic infections.

Subsequently, trials have looked at the use of zidovudine in earlier stages of HIV infection, to see if it is beneficial in people who have no HIV-related symptoms. Some studies suggested that the use of zidovudine may delay the onset of symptoms in people who are well but who have a T4 count of less than 500. However, a European study, Concorde,

Continued on page 8

Continued from page 7

which followed up participants for longer, does not appear to show any difference in the benefit of taking zidovudine alone when asymptomatic with a higher T4 count, compared to delaying taking it until either symptoms have developed, or the T4 count has fallen.

Zidovudine has also been shown to reduce the chances of HIV transmission from mother to baby during pregnancy The best way to use zidovudine appears from several studies, such as the Delta study (zidovudine/ddC or zidovudine/ddI), to be in combination with at least one other drug. During 1995, results of two studies demonstrated an advantage for combination therapy over zidovudine alone in terms of both survival, delay in opportunistic diseases and slowing of T4 decline in people with T4 counts ranging from 50-500 and both AIDS, symptomatic HIV and symptom-free infection. Importantly, combination therapy did not appear to result in a significant increase in side-effects.

It appears likely that the benefits of this type of two-drug combination therapy only last for a limited period. This may be due either to development of drug resistance or intolerance.

AZT or d4T are included in most combinations. They should not, however, be used together as they compete and lose effectiveness.

Side-effects of zidovudine

Side-effects can be divided up into transient initial problems and late effects. Early side-effects may last up to six weeks but are usually more short lived than this, and occur in less than a quarter of the people started on zidovudine.

Some of these side-effects can be helped by other medication. Early effects include nausea, insomnia and vague headaches. Late side-effects are infrequent (affecting less than 10% of people) and include anaemia, which may require blood transfusion, and myalgia (muscular aches and pains). These are reversible on stopping zidovudine. Fears of zidovudine causing cancer or even AIDS are not supported by the results of several studies, including the Concorde and Delta studies.

Zidovudine gained a reputation as a toxic drug when first used because it was given in much higher doses than are now used. Also, it was given to sicker people who are more prone to side-effects from all drugs. With lower doses and healthier people, side-effects are much less common.

ddI (didanosine, Videx)

This was the second drug to be approved for use in the treatment of HIV.

ddI is given as chewable tablets which need to be taken on an empty stomach. Because it alters the acidity of the stomach, it may interfere with the absorption of certain other drugs and vice versa. The side-effects include diarrhoea, pancreatitis (a potentially serious inflammation of an abdominal organ) and peripheral neuropathy (pins and needles or numbness caused by damage to the nerves, usually in the feet). However, these side-effects are less common at the currently used lower doses of ddI. Although the neuropathy is generally reversible on stopping the drug, some damage to the nerves in the feet may remain.

ddC (zalcitabine, HmnD)

This drug was the third nucleoside analogue to be licensed in the UK. Side-effects include peripheral neuropathy (nerve damage) and, less commonly, oral ulcers. Pancreatitis appears rare (> 1 %) with ddC.

It should be noted that peripheral neuropathy may happen to people who have never taken ddI or ddC. In some cases this is probably due to the direct effect of HIV itself. Symptoms of peripheral neuropathy, such as pains or pins and needles in both feet, present constantly over 48-72 hours, should prompt urgent discussion with your doctor.

d4T (stavudine, zerit)

d4T was licensed, based on safety data from a large expanded access programme and trials in patients heavily pre-treated with zidovudine. The role of d4T will be as a combination drug with ddI, 3TC and other drugs. It may be used in initial combinations in place of zidovudine or when a zidovudine based combination has failed.

Peripheral neuropathy appears to be the most frequent side-effects, occurring in around 10% of people with low T4 counts. The combination of d4T with ddC may increase this risk.

3TC (lamivudine, Epivir)

Licensed in 1996, 3TC (in combination with zidovudine or zidovudine + ddC or ddI) has been reported to prolong life as compared to just zidovudine alone. Combinations of zidovudine + 3TC (or d4T + 3TC) with a protease inhibitor have also been reported to have substantial effects on viral load and T4 count.

3TC appears useful in both initial and subsequent treatment regimens. Its cross-resistance profile, has led to suggestions that it should be used after ddC or ddI treatment. 3TC is very well tolerated with no increase in side-effects reported in large studies.

PROTEASE INHIBITORS

Protease inhibitors are a new group of drugs which are active at a different part of the life cycle of the virus. These drugs are potent inhibitors of HIV, including virus which has become resistant to zidovudine and other nucleoside analogues. There are currently four protease inhibitors licensed in the UK: saquinavir (Invirase); ritonavir (Norvir); indinavir (Crixivan); and a fourth drug, nelfinavir (Viracept), has just been licensed this year. All four drugs have been reported to prolong life in people experienced with zidovudine.

Continued on page 9

Continued from page 8

This class of compounds can change the levels of other drugs in the blood by altering their breakdown in the liver. It is therefore important to tell your doctor about other medication you may be taking, including 'over the counter' preparations such as antihistamines. Drugs may become ineffective or reach toxic and lethal concentrations. This also applies to recreational drugs such as Ecstasy where a fatality has been reported in association with a protease inhibitor.

Many people starting protease inhibitors experience fatigue and skin rash in the first month. This is probably due to improving immune function and the release of antiviral chemicals from immune cells. The body soon becomes used to these and you start to feel better with more energy and improved quality of life.

SAQUINAVIR (Invirase)

This was the most widely used protease inhibitor, with few side-effects and a favourable resistance profile making it attractive. However, because the drug is poorly absorbed it is probably not as potent as the other protease inhibitors. A new formulation, soft gel form, available in 1998 achieves much higher blood levels and should rectify this.

Saquinavir levels may be increased by administration with another protease inhibitor, a new strategy under preliminary investigation. Saquinavir is taken three times a day and must always be taken with food.

INDINAVIR (Crixavan)

Studies with indinavir in combination with two nucleoside analogues indicate that many patients experience very substantial falls in viral load, often maintained beyond a year of treatment. Indinavir is generally well tolerated although some people experience kidney stones. These do not need to prompt stopping indinavir and may be prevented by drinking plenty of water each day. Indinavir is taken three times a day on an empty stomach or with a low fat meal.

Changes in body shape due to the redistribution and loss of body fat have been associated with indinavir. However, it is probably an effect common to all the protease inhibitors. Virus which becomes resistant to indinavir is often resistant to a range of other protease inhibitors. Therefore compliance (taking 100% of tablets on time), which limits the chances of resistance, is critically important.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIS)

This class of drugs includes nevirapine (Viramune), and delavirdine (Rescriptor) are currently licensed. But DMP 266 (Efavirene) is currently unlicensed but is available through special access programmes or trials.

It is uncertain how these drugs should be best used. They are less potent than protease inhibitors and resistance can develop rapidly unless viral replication is effectively suppressed. They are frequently used in initial regimens to save the protease inhibitor class for later. They may also be useful when other drug treatment has failed.

The most common side-effect is a rash which may be severe. This appears to be less with DMP 266.

OPPORTUNISTIC INFECTIONS AND THEIR TREATMENT

PNEUMOCYSTIS CARINII

Pneumonia caused by the fungus Pneumocystis Carinii (PCP) is the commonest opportunistic infection in developed countries.

The main features are a gradual onset of dry cough, breathlessness and fevers. Investigations needed to diagnose this condition and assess its severity are a chest X-ray, a special sputum test and a blood sample taken from an artery (to measure gases in the blood). The doctor may also ask you to go on an exercise bike whilst measuring your oxygen levels (exercise oximetry). Sometimes a bronchoscopy is needed to make the diagnosis. This involves passing a thin fibre optic instrument into the lungs through the nose. This procedure is carried out under sedation.

There are several available treatments for PCP. The commonest is co-trimoxazole (Septrin, Bactrim) which may be given intravenously as a drip or as tablets, depending on the severity of the infection. Co-trimoxazole may cause nausea which can usually be controlled with anti-sickness pills. Rashes are also common with this drug.

Other drugs commonly used include pentamidine (Pentam, NebuPent), clindamycin with primaquine, dapsone with trimethoprim, and atovaquone (Wellvone). All these drugs have some side-effects which should be explained to you by your doctor if they prescribe them.

PCP is a preventable infection. If you develop certain symptoms and/or your T4 count reaches a certain level (usually less than 200, or 15%), your doctor will recommend starting preventive treatment. This is called prophylaxis, and several regimes are available. The commonest are co-trimoxazole, dapsone or inhaled pentamidine. They are given in low enough doses to minimise side-effects but large enough to ward off PCP.

TUBERCULOSIS

Tuberculosis (TB) and related infections are common in people with AIDS. Symptoms including cough, fever, sweats and weight loss are suggestive. People from overseas, where TB is more common, are at greater risk and may be offered a skin test (Heaf or Mantoux) and chest X-ray to screen for this. A previously rare form of TB called Mycobacterium Avium Intracellular (MAI or MAC) may be seen in people with AIDS. It is a generalised infection which may be first found in blood, stools or samples specially taken from the liver or bone marrow. The symptoms are

Continued on page 10

TREATMENTS AND DRUGS IN HIV

Continued from page 9

non-specific with weight loss, night sweats, diarrhoea and anaemia, often in someone who has had AIDS for some time. Treatment usually involves a combination of several antibiotics, usually taken for at least six months, and possibly for life. Some antibiotics, rifabutin (Mycobutin) and clarithromycin (Klaricid), and azithromycin (Zithromax) may be useful in preventing the development of MAI. However their use is not currently widespread in the UK. Also, in London there has been a recent outbreak of TB resistant to usual treatments. If you have been in contact with someone with TB and have any chest symptoms it is important to inform your doctor.

CYTOMEGALOVIRUS

Cytomegalovirus (CMV) causes problems in advanced disease when there is profound immunosuppression. It most commonly effects the eye (retinitis) but may affect the gut, brain or lungs. Any eye symptoms should prompt urgent medical consultation. Some clinics offer regular screening by an ophthalmologist when the T4 count is low (i.e. < 60).

Because CMV soon returns if treatment is stopped, medication is maintained lifelong. The most established treatments are given intravenously on a daily basis (i.e. ganciclovir and foscarnet). An oral preparation of ganciclovir is licensed and this may be used after the first two to three weeks of intravenous therapy. Other preparations being used include cidofovir which has the advantage of being administered every one to two weeks instead of daily. Injections and implants into eyes also look good

If intravenous therapy needs to be maintained, then permanent access through a Hickman line or Portacath will be achieved through a simple operation. This avoids the need for repeated use of a needle to find a vein.

Side-effects of ganciclovir include lowering of the blood count. Foscarnet and cidofovir can affect kidney function. While taking these drugs your clinic will monitor you to detect any adverse reactions.

THRUSH

Thrush or oral candida is a common fungal infection of the mouth. It usually appears as a thick curd-like coating on the tongue, gums and palate. It often develops after a course of antibiotics and may be more common in smokers. It is generally easy to treat with either lozenges, mouth washes or tablets.

The tablets include ketoconazole (Nizoral), fluconazole (Diflucan) and itraconazole (Sporanox) which all work equally well. A short course (e.g. five days or less) is all that is needed. In the rare event that the infection keeps recurring, your doctor may recommend taking tablets more regularly. Candida can also affect the gullet. This causes difficulty and discomfort on swallowing. The treatment is the same, and provides rapid and effective relief of symptoms.

ORAL HAIRY LEUCOPLAKIA

Oral hairy leucoplakia (OHL) is an infection caused by the glandular fever virus (Epstein-Barr virus) on the side of the tongue where it causes white hairy looking marks. There are no symptoms and the infection comes and goes. It is not thought to be infectious and no treatment is needed.

SHINGLES AND HERPES

Shingles (Herpes zoster) is a reactivation of previous chickenpox infection and occurs in a nerve distribution producing a 'band' of blisters on the face or body. There are often associated aches and pains and itchiness. This is treated with a high dose of the anti-herpes drug acyclovir (Zovirax) or the similar drugs famciclovir (Famvir) or valaciclovir (Valtrex) together with painkillers, and it usually then resolves over a couple of weeks. When present, shingles is highly infectious to people who have not had chickenpox.

Recurrent cold sores and genital herpes (both caused by Herpes simplex virus) are common problems for people with HIV. They can be successfully suppressed by taking acyclovir tablets, and some studies have shown that this treatment may have a beneficial effect on HIV disease itself.

TOXOPLASMOSIS

Toxoplasmosis is a protozoan infection which usually causes abscesses in the brain. These abscesses can produce symptoms of headache, fits, weakness or numbness in a limb, or confusion. Toxoplasmosis can be diagnosed by carrying out a CT or MRI brain scan. Treatment is with a combination of drugs, e.g. sulphadiazine or clindamycin with pyrimethamine, often with a course of steroids. Treatment is for several weeks until improvement has occurred and the drug doses can then be reduced to a preventative level.

Toxoplasmosis is currently not a common infection in the UK. Its main host is cats, so care must be taken with these pets, particularly when cleaning up their litter. It is also important that meat should be well cooked. However, in most cases toxoplasmosis occurs as the result of infection acquired in childhood.

Cryptococcus is an opportunistic infection in people with AIDS which usually causes meningitis with fevers, headache and neck stiffness. The standard treatment, the drug amphotericin, is highly effective. However, it is often difficult to tolerate as it causes chills, agitation and kidney problems and needs to be given as a drip.

The alternative is to use fluconazole which is also very effective in intravenous or oral form. Once treatment has been successful a preventative dose of oral fluconazole is given, lifelong, usually at least 200 mg or 400 mg daily.

Please note that treatment and drug therapy changes rapidly. Some of the information will become out of date or it may be new to your centre. So check first.

My thanks to AVERTS for information

Football, is it More than Just a Game?

What to write about for a change? I thought as I sat at the keyboard of my Apple Mac one sunny Thursday afternoon. How about another story of hardship and pain, perhaps a piece about coming to terms with my illness and all of its eccentricities; or maybe a line or two about Professor De'ath and when I expect him to come and claim me.

Then I thought Bollocks! Let's put something down that's positive [no pun intended] and upbeat for a change, so that's exactly what I did.

Can you remember when you were able to actually move at more than a snail's pace, before the arthritis in your ankles and knees prematurely turned you into an old git?

The days of playing football for hours on end in the park with all your mates. Football, glorious football! There is nothing better on earth for me than the glorious game. People say it's just a game, twenty two blokes chasing a piece of leather, full of air, around a field.

They are entitled to their opinion however wrong they may be. Since the onset of dodgy ankles I haven't been able to kick a ball properly for many a year, and it is in this time that my interest has gone into helping my son develop his game.

Watching him as an awkward eight year old, little did I realise that the next four years would be spent watching him train weekly, and spending every Saturday morning (ankle bleeds permitting) standing on the side of a windswept pitch somewhere in the valleys of South Wales, cheering him on.

Watching these kids playing and enjoying the game regardless of who wins, has helped me a lot. Through times of depression and blackness, seeing their enjoyment was the only thing that kept me going.

Football more than just a game.

I think it is.

Legal Highs!

BY MR. D MONO

Legalise pot and do it today
You know it makes sense it is the right way
It can treat glaucoma and asthma too
Don't listen to the politicians they're lying to you.

I've never robbed anyone or mugged an old man,
Never stolen from single parents like "Tory Blur" can.
But the law says I'm a criminal for smoking grass
That old saying's true 'the law is really an ass'

To class it with smack, speed and cocaine,
I think those law makers have damaged they're brains,
Especially when you think that those addictive three
You can get from you're doctor quite legally.

Since man walked the earth this weed has been used,
To treat many ailments and help stop the blues,
Queen Vicky, she took hemp to ease the strain,
When she felt the cramps, of menstrual pain.
New labour, new Drugs Tsar, same old lies,
I look at the fools with contempt in my eyes.
The evidence is there for all to see
But they're covering up mysteriously.

Cos', you can't have medicine you can grow for free
Because there's no profits for the pharmacy.
You can destroy your liver, with whisky and beer,
Or murder your lungs with fags without fear,
You can even eat meat that will rot your brain,
But you can't take cannabis to ease the pain.

"Hard drugs will follow!" is their battle cry,
But that is misleading, I'll tell you why,
If you have to meet drug dealers to buy your hash,

Then some of them just want your cash,
To you then they will try to sell
Those lethal drugs that make life hell.

So if the people want to buy,
Cannabis to get them high,
Let them do it legally,
Then less hard drugs you're sure to see,
So smoke it or eat it or drink it in tea,
It will ease your arthritis I think you'll agree.

Who Wants to be a Mad Cow or Sheep

CJD – theoretical or real risk?

Final confirmation by the Department of Health for alternative sourcing was announced via a press release on the 13 May 1998 — "Committee on Safety of Medicines Completes Review of Blood Products." It requires BPL to begin processing its range of products from qualified US plasma.

« The NHS Bio Products Laboratory and the SNBTS' Protein Fractionation Centre have been advised to take steps to source products from plasma derived from outside the UK, while giving due regard to the supply of vital products to patients.»

UK BLOOD PRODUCTS

Since the indentification of nvCJD by the CJD Surveillance Unit in Edinburgh, there has been much speculation about its prevalence, infectivity, transmissibility and any risk it might pose to the safety of the UK blood products supply.

In the past half-year, the pace of government investigations into this issue has increased significantly, attracting a good deal of attention but yielding few clear answers.

What has been revealed is the commitment of all regulatory authorities to maintain the unequivocal safety profile of UK blood products. Bio Products Laboratory, part of the NHS since 1950, shares this commitment and is taking the necessary steps to minimise the theoretical risk posed by nvCJD.

To help make sense of the events surrounding the nvCJD issue and the recent regulatory announcements and to share its plans for the longer-term future, BPL has undertaken to hold a series of informal seminars to discuss the issues with healthcare professionals involved directly or indirectly with blood plasma products.

nvCJD AND SAFETY MEASURES – A RECENT CHRONOLOGY

Up to April 16 this year, there have been 24 recorded deaths from nvCJD in Britain: three cases in 1995, 10 each in 1996 and 1997 but only one recorded case this year, in February.

The issue of plasma product safety came to the fore when three of the first 23 nvCJD victims were identified as blood donors. This identification resulted in plasma product recalls last Autumn. While the risk of transmissibility was recognised as theoretical, recalling product was the only sure way to remove any potential risk.

There is evidence that the current production processes used by BPL have the capacity to remove the (assumed infective) prion from blood plasma.

However, as there is no detection test, this expectation cannot be validated and the recall of products made from a plasma pool containing a donation from an nvCJD patient is likely to recur.

These recalls would undermine not just the public's confidence in plasma products but the whole of the NHS blood service.

The view of the UK Haemophilia Centre Directors was presented in November 1997. Regarding plasma-derived Factor VIII, they revealed their strong preference for non-UK plasma as the source.

Mr Dobson also announced the outcome of a review of the NHS's provision of the blood product Factor VIII, used in the treatment of haemophilia. He said: "The Haemophilia Society, amongst others, have highlighted their concern about blood borne infections and, in particular, the effect which those concerns have on families with haemophiliac children.

Though the risk of nvCJD transmission is hypothetical, nevertheless the fear of it is very real to this group which has previously been affected by both HIV and Hepatitis C (virus) transmitted from Factor VIII. 'So I have decided that all health authorities must make arrangements to ensure that the synthetic version of Factor VIII, known as recombinant, is made available to those children under the age of 16 who are not already receiving it, and to new patients."

In February 1998, the The CPMP, which is the European Committee on Proprietary Medicinal Products, (it advises the European Commission on regulatory matters in a specific group of pharmaceuticals, notably those derived from biotechnology and high technology,) met to tackle the many sub-issues associated with nvCJD. It delivered a statement saying that UK albumin should not be used as an excipient in vaccines (because of extremely wide usage).

The statement was reinforced in the UK by the DOH and the CSM. The CSM increased the possibility of recalls of blood products by extending them to include products made from donors "strongly suspected of having nvCJD" as well as "confirmed cases". The precautionary climate was heating up.

It was in this environment several months ago, that the DOH released a statement which allowed BPL to investigate the viability of using plasma from outside the UK. BPL rose to this challenge as it allowed the organisation to continue to manufacture safe products.

As these discussions, recommendations and precautionary measures unfold, it is important to keep in mind that it is not simply a question of risk or non-risk, but a delicate balancing act.

While there is a fear of possible nvCJD, there is a real threat of death or other patient morbidity if appropriate plasma products are not available.

BPL is now poised to begin importing plasma from qualified centres in the US and has taken the necessary steps to ensure that the ongoing needs of UK patients will continue to be met.

Fatigue

Trying to stay awake

If you feel excessively tired, or you have trouble doing everyday tasks, you may be experiencing HIV-related fatigue. Fatigue is common among people with HIV. Many people simply put up with fatigue, however it can be treated. How you tackle fatigue depends on the cause. There are a number of causes of fatigue which are discussed below.

HIV AS A CAUSE OF FATIGUE

HIV is a chronic (long-term) infection and the body mounts a strong immune response against it. People with HIV may use a lot of energy because they are constantly battling the virus, so fatigue may slowly develop as a consequence of HIV itself.

High viral load is particularly associated with fatigue. Combination therapy often slows HIV production in the body and many people have more energy after taking anti-HIV drugs.

HIV-RELATED MEDICATION & FATIGUE

Even though anti-HIV drugs may improve energy levels, some may also cause fatigue, especially in the first few weeks of therapy. Certain drugs, including AZT, may cause fatigue by slowing the production of red blood cells (which carry oxygen around the body).

If you suspect one of your anti-HIV drugs is causing fatigue, you may wish to consider switching drugs. First, rule out other causes of fatigue and consider all your treatment options. Drugs used to treat opportunistic infections (such as co-trimoxazole, dapsone and pyrimethamine used to treat PCP and toxoplasmosis, and ganciclovir used to treat CMV) may also cause fatigue. Folinic acid may be taken as treatment.

If your fatigue is due to drug treatment, and you can't stop taking the problem drug, you can be treated with a blood transfusion. This gives you a quick burst of red blood cells, but it is not a long- term solution. Transfusions have a number of disadvantages such as the transmission of infections including CMV. Another short-term option may be injections of a synthetic hormone called erythropoietin which stimulates the production of red blood cells. There can also be a reduction of white cells caused by some HIV drugs stopping the bone marrow producing the cells. This will cause tiredness, but can be remedied by small injections (sub-cutaneous) of GCSF (Granulocyte Colony Stimulating Factor).

VITAMIN & MINERAL DEFICIENCIES

Fatigue may be caused by low levels of certain vitamins and minerals. A nourishing, balanced diet may reduce fatigue. Consult an HIV dietitian about minimising fatigue through dietary changes and supplements. For further information see NAM's Nutrition booklet. Even if you are eating well, you may not be absorbing the goodness from the food you eat due to diarrhoea, stomach bugs or opportunistic infections. Your doctor can investigate and treat the cause of vitamin and mineral deficiencies.

SLEEP, STRESS AND DEPRESSION

Fatigue may be a consequence of disrupted sleep patterns. You may want to establish a routine that balances work, relaxation, sleep and socialising. Consider complementary therapies such as massage or acupuncture to relieve anxiety or fatigue. Reducing your intake of coffee, alcohol and recreational drugs may also reduce fatigue.

Stress and depression may cause fatigue. Consult your doctor about medication or counselling.

OTHER MEDICAL CAUSES OF FATIGUE

Some opportunistic infections (e.g., MAI and TB) and cancers can lead to fatigue and chronic pain. Treatment should be directed at the infection. Low levels of testosterone may cause fatigue. Steroids may be used to give you energy and build muscles, in conjunction with regular exercise.

OTHER ACTION TO REDUCE FATIGUE

You can take action to enhance your energy levels. Moderate exercise improves energy levels and immune function, so you may consider an appropriate exercise routine. Re-organising at home and work may save your energy e.g., put items within easy reach, sit while preparing meals.

Haemophilia, HIV & HCV

The Triptych BY NIGEL HUGHES, CLINICAL NURSE SPECIALIST HIV & VIROLOGY

Co-infection with HIV and HCV is now a significant issue for those living with haemophilia globally, but the impact of this dual epidemic has only more recently been researched and evaluated. There are diverse questions for individuals living with this triple problem and the services and physicians that support them. Amongst them are key issues surrounding infectivity, prognosis, monitoring, therapy and outcomes and the interactions and pathogenesis of HIV and HCV.

INTERACTION BETWEEN HIV & HCV

It has been estimated that haemophiliacs infected with HIV/HCV are twenty-one times more likely to develop liver failure than HIV-/HCV+ haemophiliacs and 30 times at more risk of developing liver cancer (HCC) than the general population. The interaction between the viruses is still relatively poorly understood, but more recently there are some indications of how these viruses interact and affect those individuals infected with both. It is particularly important to note that although these are two distinct viruses, causing distinct disease processes, they have very similar properties and characteristics.

Globally both HIV and HCV are isolated as diverse genotypes or "strains". HIV in two major genotypes, HIV(1) and HIV(2) with 12 subtypes of HIV(1) and 5 subtypes of HIV(2) so far discovered. HIV also has the ability to create "mosaic" viruses with shared genetic material between subtypes and within an individual "swarms" of viruses known as quasispecies, created over a period of time as the viruses mutate within the host. HCV also has a diverse genetic identity globally, with 6 major genotypes and 80 subtypes discovered so far. It also mutates readily within an individual, creating quasispecies and the viral turnover per day is approximately equivalent to or higher than the viral turnover of HIV. By learning from the studies of HIV we have gained greater insight into the natural history of the Hepatitis C virus. We also have more insight into how HCV interacts with the host and in particular the liver, the main site of viral activity and replication. It has been suggested that genotypes 1 and 4 are more resistant to interferon therapy and both may have an associated higher risk of liver disease., but this remains debated.

VIRAL REPLICATION

We are beginning to understand how this virus reproduces within the body. All viruses want to reproduce, but require a host to use as a viral factory. HCV seems to infect certain identified cells within the body, mainly hepatocytes (liver cells), lymphocytes (certain white blood cells), cells within the spleen and possibly the bone marrow. There is uncertainty as to how the virus invades the cell, but as HCV has an affinity for lipids ("fats"), it may use lipid receptors on the cell wall. Once inside it uses an enzyme called "Helicase" to translate its RNA. Unlike HIV, this virus does not integrate with the host cell's DNA in the nucleus.

After this process HCV uses the cell's internal factory, called the Endoplasmic Reticulum to build all the viral proteins to assemble new viruses. A protease enzyme (similar, but not identical to the HIV protease) is then used to mature these new viruses which "bud" out of the cell and infect new cells. We do not understand how HCV causes cells to become cancerous, but we now have an understanding of how HCV fibrosis in the liver also results in fatty changes to the liver structure, as it manipulates the lipid stores within the cell. HCV may use lipids to protect it from the immune system, as it can be detected in the blood with a lipid coating.

HCV also circulates as multiple "quasispecies" or "swarms" with genetic variation, and this increases in some individuals the longer they are infected. Quasispecies may be formed as a mechanism to allow HCV to escape immune detection, to give it an edge in survival and replication or due to so-called "selection pressure" governed by the immune response or the use of anti-viral therapy.

The viral turnover and replication rate for both HIV and HCV are relatively similar, but the interaction between the two is not well defined. Research into the interaction between HIV and Human Herpes Simplex Virus 6 (HHSV6) may yield some insight, as Robert Gallo suggested that novel variants were isolated that were the recombinant viruses of both original viruses in the same host. Is this a clue to the interaction of HIV and HCV? *(Another Gallo Guess! Ed.)* This is still unknown, but alternative possibilities include HIV/HCV co-infection causing an immunological response that results in altered dynamics and disease progression.

In a comparison between HCV+ haemophiliacs and HIV/HCV+ haemophiliacs the rate of increased HCV RNA was a ratio of 3:58, with the HIV/HCV+ haemophiliacs having demonstrably higher HCV RNA "viral loads" and by inference a more dynamic and upregulated HCV replication rate. How this process occurs is unknown. It may be linked to the concurrent immunodeficiency of the accompanying HIV disease allowing a higher HCV replication rate, or a direct interaction between HIV and HCV, but again this is unknown.

Several studies support the evidence that HCV RNA levels are increased in HIV/HCV+ haemophiliacs compared to HIV-/HCV+ individuals. There is also evidence to suggest this is worsened in HCV+ haemophiliacs infected with HIV subsequent to their HCV infection and in older haemophiliacs infected in

continued on Page 15

later life. The possibility of reduced immune response to HCV in the HIV+ haemophiliac with demonstrable immunodeficiency and increased RNA levels may also be associated with increased quasispecies diversity of HCV viral populations in the HIV/HCV co-infected haemophiliac individual.

NATURAL HISTORY OF HIV/HCV CO-INFECTION

The majority of current research supports the hypothesis that HIV/HCV co-infection results in a significant risk of increased liver disease and a potential for increased infectivity. This is a generic risk for all HIV/HCV co-infected individuals irrespective of transmission routes, but the majority of studies have been performed in the haemophiliac population. These studies suggest a particular increased risk of progression in haemophiliacs to liver disease and liver cancer.

The increased progression may be associated with the introduction of HIV infection into individuals with prior HCV infection, or that certain HCV genotypes, particularly genotype 1a and genotype 1b in the UK may be associated with more significant risk.

In the HCV+ individual without co-infection with HIV the average risk of cirrhosis is 20-25%, with a 10-15% risk of hepatocellular carcinoma and 1-3% mortality rate per annum. The increased risk of disease in HIV/HCV+ individuals must be viewed as worrisome if the trend of disease is higher than in the HCV+ population alone. There is evidence to suggest that haemophiliacs with advanced HIV disease require significantly higher quantities of clotting factors and advanced liver disease due to chronic HCV infection will similarly exacerbate this.

Certain factors may be associated with increased risk of liver disease progression:

- Age and infection in later life;
- Male gender;
- High HCV viral load;
- Genotype 1a or 1b;
- Severe HIV disease/AIDS related diseases.

There are many debates about HCV viral disease or non-hepatic manifestations of HCV. The most pre-eminent symptom associated with HCV infection and not necessarily associated with the extent of liver disease is fatigue. Associated diseases include autoimmune disorders, particularly mixed essential cryoglobunaemia, sialadenenitis, porphyria cutanea tarda and possibly other diseases such as non-Hodgkin's lymphoma and diabetes mellitus. [See Hughes N; Hepatitis C - not just liver disease (Part One & Two); Mainliners Newsletter 1997; October & November]

A number if studies have demonstrated a poorer quality of life in HCV+ individuals when compared with other client groups with chronic diseases such as diabetes mellitus or hepatitis B, and the healthy HCV negative population controls.

DISEASE PROGRESSION & THERAPY

The majority of studies with significant cohorts of HIV/HCV+ haemophiliacs suggest that there is a lower response to standard Interferon monotherapy of 3-6 million units thrice weekly for 6-18 months. The effectiveness of Interferon Alpha and the anti-viral agent Ribavarin have yet to be fully evaluated in a prospective and large scale trial, but it is hoped that the improved response rate to dual combination therapy in HCV+ clients will be seen in HIV/HCV+ haemophiliacs.

Therapy for non-hepatic manifestations are not well described with conflicting findings in relation to effectiveness of standard therapies in reducing symptoms and disease, but the best characterised is the response to Interferon monotherapy in mixed essential cryoglobunaemia, which is generally significant. Overall it is thought appropriate to stabilise HIV disease initially with combination anti-HIV therapy and to initiate standard anti-HCV regimens between six to twelve months after CD4/CD8 counts and HIV viral loads have stabilised.

One of the other contentious issues facing HIV/HCV+ haemophiliac is the need for a liver biopsy. Unfortunately it remains the only method to assess and grade the degree of inflammation, necrosis (cell death) and fibrosis (scarring). Liver disease can then be graded as mild, moderate and severe with the mild and moderate client groups responding better to therapy as a rule, but the moderate and severe groups more likely to progress to significant morbidity and mortality.

Several studies have illustrated the benefit and suitability of liver biopsy with the appropriate clotting factor prophylaxis regimes, but other methods including ultrasound, laporascopy and alpha fetoprotein assay for liver cancer may be useful alternatives for long term methods of evaluation of liver disease progression.

Unfortunately recent studies suggest a potential intolerance of HIV protease inhibitors in HIV/HCV+ individuals receiving Highly Active Anti-Retroviral Therapy (HAART). Hepatotoxic reactions were more common in HIV/HCV+ individuals receiving the protease inhibitor Indinavir (Crixivan), although they remain a minority of individuals.

Chronic HCV is an independent predictor of hepatotoxocity and is more prevalent in individuals with HIV co-infected via injecting drug use or haemophilia. Other protease inhibitors were apparently indicated less in this side effect, but full and larger studies to evaluate the problem are needed.

BIRCHGROVE IS A FORUM FOR:

- **The treatments of haemophilia and HIV**
- **Taking care of ourselves, through informed debate and argument**
- **Staying healthy with Haemophilia HIV & AIDS and HEP C**
- **Ways in which HIV affects love and sexuality**
- **The social and psychological aspects of haemophilia and HIV**

PEOPLE WITH HAEMOPHILIA AND HIV

- **Can be empowered and enabled to deal with HIV/AIDS through relevant information and mutual support**
- **Can improve their health and extend their lives by expressing feelings and confronting the issues directly**
- **Should be heard and have their needs recognised and not suffer in fear and isolation**
- **Have a role in the work of the HIV/AIDS community to inform and challenge the ignorance that exists about HIV**

Available from the Birchgrove Group, free of charge to those directly affected by Haemophilia/HIV or registrants, are the following information leaflets and back issues of the Birchgrove Newsletter.

Birchgrove Newsletter Back Issues

- ❑ BIRCHGROVE newsletter *Issue 5*
- ❑ BIRCHGROVE newsletter *Issue 6*
- ❑ BIRCHGROVE newsletter *Issue 7*
- ❑ BIRCHGROVE newsletter *Issue 8*
- ❑ BIRCHGROVE newsletter *Issue 9*
- ❑ BIRCHGROVE newsletter *Issue 10*
- ❑ BIRCHGROVE newsletter *Issue 11*
- ❑ BIRCHGROVE newsletter *Issue 12*
- ❑ BIRCHGROVE newsletter *Issue 13*

Birchgrove Information Leaflets

- ❑ Hepatitis C – Special Edition

We can also supply the following items.

❑ "Living with Haemophilia and HIV"	£2.50
❑ Red Ribbons (Cloth)	£0.50
❑ Red Ribbon Badges (Enamel)	£2.50
❑ Birchgrove Red Ribbons (Enamel)	£2.50

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Send to:

The Birchgrove Group,
PO Box 9, Abertillery, NP3 1YD.
or Phone 01222 387960 Helpline
01222 373560 Admin./ Fax

The things they don't say?

I feel that I'm one of the lucky ones who has a good relationship with all medical professionals looking after my treatments and care. We are able to sit down and discuss all problems and issues surrounding Haemophilia HIV/AIDS and if I'm really bored – HCV.

We spent over two years going through the pros and cons of taking combination therapy and I was finally forced into going onto a regime because I was told I could be dead within three weeks. I was feeling really ill and my quality of life had gone.

So I started taking The Pills. The first combination was a total waste of time – with sickness, the trots, and seeing no improvement in my health.

Then after the conference in Bath, I was taken into hospital with PCP, and the first combination was stopped. After a few weeks of septrin and yet another cocktail of different drugs, I was put onto a new combination, less drugs; easier to take; and after a while I started to feel better.

My health has continued to improve and I can stick to The Pills with no problem of compliance (Ha! Ha!).

But what really pisses me off is the little things you are not told before you start taking these things - uncontrollable itching which can blister when scratched. So you're given some steroid cream to stop the itching and some antihistamine to help with the reaction, but they don't tell you that the cream stains all your clothes and bedding and the steroids keeps you awake most of the night – for some reason.

But the good news is I'm on the mend. Some people might say it's not good news but . . .

I'm back.

Gareth