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MEETING REPORT

FORUM ON MANAGEMENT OF FACIAL FAT LOSS AND ACCESS TO POLYLACTIC ACID (PLA, NEW-FILL) IN THE UK

24th January 2002, London, UK

Meeting hears calls for NHS funding and training to provide repair treatment for people with facial lipoatrophy

Graham McKerrow, HIV i-Base

A meeting of more than a 100 doctors, nurses and patients at the Royal Society of Medicine in London, heard repeated calls for the National Health Service to offer New-Fill treatment to people with facial lipoatrophy (fat loss). Speakers called for advice on the use of New-Fill to be included in the official guidelines on treating HIV, for political pressure to be exerted on the NHS to pay for this treatment, and for the establishment of a contact forum where people who are considering the treatment would be able to talk to those who have had it.

The meeting, organised by HIV i-Base, publishers of this journal, and the Royal Free Hospital in London, heard from people who said lipoatrophy had caused them a range of social and psychological problems. One man said he had been turned down for jobs because of it, and a woman spoke about spending a morning weeping in front of a mirror.

Patients and medical professionals were united in calling for the health service to provide treatment. All the HIV commissioners for the London health authorities – the NHS managers who decide what the health budget will be spent on – were invited to the meeting, on 24 January, but none attended. One man with lipoatrophy told the morning session: "I am very disappointed the commissioners aren't here today; I'm very angry they aren't here today." However, there was a round of applause for the presence of Barbara Disney who works for the London Borough of Camden and is a senior development officer representing the local authorities on the London Health Authorities Commissioning Group.

Speakers urged patients and professionals to lobby the commissioners to pay for the treatment – which consists of injecting New-Fill – a hydrogel of Polylactic Acid (PLA) - into the face to improve facial appearance of people who have lost fat. People were encouraged to lobby their MPs to put pressure on the commissioners. Some speakers called on the British HIV Association (BHIVA) to lead the way. Dr Mike Youle of the Royal Free Hospital, London, said: "What we need to do is unlock the money and train the people to do it." A man from Liverpool said the cost of PLA should be included in the budget for HIV care.

Several people spoke about being treated by Harley Street doctors where the treatment costs £400 to £500 a session and commonly requires three to six sessions.

The meeting heard reports from around the country of what is happening in the NHS; several hospitals are running trials while some are siphoning money from other budgets to treat a small number of people. Speakers included doctors from Paris who have extensive experience of treating people with PLA and a plastic surgeon from New York who outlined other options, particularly transplanting fat from other parts of the body.

French patient survey reveals demand for PLA and need for information

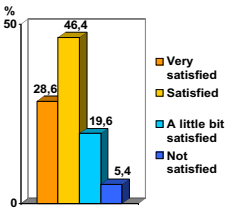
Emmanuel Trenado of the organisation AIDES in Paris outlined the results of a patient survey he carried out in France at the end of last year, in which 248 patient-completed questionnaires were analysed to evaluate the need for and the obstacles to treatment, and to collect reports of patient satisfaction with treatment.

Of those surveyed, 84.7% were men; most were aged between 30 and 49 years and had been positive for more than 10 years. More than 67% had been on antiretroviral therapy for more than five years. They suffered from prominent veins and loss of body fat and buttocks. Almost one in four, 23% said they could not discuss the problem with their doctors. Only 23.4% said they had access to 'repair procedures'.

Of those who had been treated, 67.9% had been given filling products such as PLA, and 91.1% of them were treated in 2000 or 2001. Nearly three out of four, 72.5% were given PLA, and 12.5% were given Hyaluronic Acid (Restilane and Perlane, for example). Most (51%) of those who had been treated with filling products had three to five injections. Only 9.8% required more than five injections.

The overwhelming majority, 86.8% said they tolerated the procedure 'well' or 'very well'. Seventy five per cent of responders were 'satisfied' or 'very satisfied' with the results of the repair procedure and 5.4% said they were not satisfied, mainly because of insubstantial filling effect or the cost. Of those who did not access treatment, 50.8% said it was because of a lack of information and 39.6% said it was because of the cost. Most, 86.9%, said they wanted access to the treatments. Almost 80% wanted filling products rather than surgery or other types of treatment.

Were responders satisfied with the repair procedures?



Overall, 75% of responders are satisfied or very satisfied with the results of the repair procedure.

25% of responders are not satisfied (mainly lack of filling effect or price issue).

Trenado concluded that the vast majority did not have, but wanted, access to repair procedures. Filling products were the repair procedure most commonly used. The responders who had undergone the repair procedures were pleased with the results. The study found a need to better inform people about facial lipoatrophy, and a need to address the question of how treatment would be paid for.

Mike Youle, who was chairing the meeting, pointed out that treatment in the UK was approved on an individual hospital basis, and its availability depended on how much people lobbied for a particular treatment, whereas France has a much more even provision across the country.

Limited availability of PLA in the UK

Some hospitals in the UK are already offering treatment to a few patients and it was stressed that when available this was only to existing patients. Doctors reported the following pattern of provision:

University College Hospital, London. Dr Ian Williams said the Mortimer Market Centre was working with colleagues in plastic surgery and hoped to provide PLA and collagen. They are seeking funding for this.

North Manchester General Hospital. Dr Ed Wilkins said they had set up a study, and 33 patients had received injections of PLA. He was trained in the procedure by Dr Elizabeth Laglenne from Paris, who also spoke at the meeting. He said it was a relatively simple procedure to learn and administer, although there was some debate among the medical professionals at the morning session about whether it should be carried out by HIV doctors, nurses or plastic surgeons. The Manchester study is looking at the quality of life implications of treatment, as well as measuring the physical results by scanning the thickness of the skin before and after treatment. He said that so far 75% show a good improvement and 25% a very good improvement. They have applied for funding.

St Mary's Hospital, London. Dr George Scullard said they were working with dermatologists and were about to treat between 20 and 30 people.

Chelsea and Westminster Hospital, London. Charge Nurse Sharon Brown reported that many more people required the treatment than could be found places on the pilot scheme they are running.

East London. Dr Tom McManus of Newham General and the Royal London, said they were investigating fat transfer work with the New York plastic surgeon Dr Jeff Brande, but there was "no interest" from the local NHS commissioners.

King's College Hospital, London. Dr Chris Taylor said they were exploring ways of funding treatment.

Royal Free Hospital, London. Dr Youle said they had approached a plastic surgeon colleague and had been planning to work together but the plastic surgeon has moved to another job. They would take the matter up with the new plastic surgeon, and Dr Youle said: "I think this will be in our next year's budget."

Ealing Hospital. Dr Stephen Ash said he had treated 12 people with PLA, and added: "So far the patients are very happy with the outcome." The treatment has been paid for by taking money from another budget. Dr Ash added: "It would help if it was in the BHIVA guidelines."

The doctors emphasised that treatment was only available for a limited number of registered patients, and that this treatment would not be available to new patients who were switching treatment centres solely to access New-Fill.

People with facial wasting tell of trauma, and the need for repair treatment

A substantial part of the meeting was devoted to discussion by patients about the consequences of having facial lipoatrophy and the experiences of those who had received repair treatment. Bryan Thompson said: “It was literally a three month period where my face just began to fall off. The thing about facial lipoatrophy is that it blows your cover; people realise. Every day it was there and a constant reminder that I was HIV positive.

Kate Thomson, told the meeting about being in tears over the way she looked and the lack of information about treatment: “I looked like I had aged about 20 years in a matter of months. Today is the first time I have met anyone who has had the procedure and we need to get the information out there so that people can access it.” She said she had had to deal with advice from people who thought she was anorexic.

One man, an actor by profession, had a course of three injections at the Chelsea and Westminster Hospital “and I can’t wait for the fourth one.” When he developed lipoatrophy, he was shocked by his facial appearance, and “devastated” when he saw his mother’s reaction. Lipoatrophy had cost him work; at one point his agent said to him: “There is no way you can do anything with a face like that.” He said: “I am really grateful I got onto the [PLA] trial. I think it should be available for everybody because it does make a huge difference.”

French doctors outline the advantages of PLA

Dr Elizabeth Laglenne of Paris, who has worked for 20 years with silicone and other implants made one of the most impressive contributions to the meeting. Seven years ago she learnt about PLA and started using it. She said there is more information on it than some people think; there have been studies conducted in the Netherlands, Belgium and other countries, as well as in France.

Fillers like PLA and collagen are good for people who don’t have any fat to transplant, she said. Collagen requires a lot of injections and is more expensive than fat transplants or PLA “and it is too difficult”. She said: “New-Fill has been on the market for a few years and we have followed it for three years after treatment.”

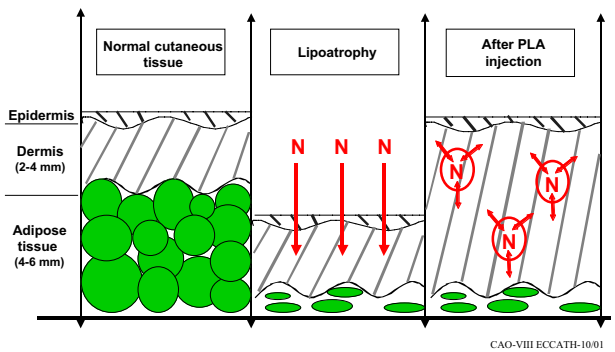
Dr Laglenne said: “If you have money, you can pay for treatment but we must do something for the most important population: people without money.” As well as seeing private patients, she has also treated 500 people without charge, such is the demand. She said the treatment is getting better as techniques are improved; for example they now slightly dilute the product to make the injections easier and to give a smoother result. Some people have complained that the injections hurt, but this can be relieved by first applying an anaesthetic cream to the skin and also including an anaesthetic mixed into the product.

Also from Paris was Dr Camille Aubron-Olivier of the Hôpital Pitié-Salpêtriére, who reported on the Vega study of the safety and efficacy of PLA treatment in positive people with severe facial wasting. It is an open label, two centre, pilot study, which started in May 2000 and is following 50 patients for 24 months. Patients attending the Hôpital Pitié-Salpêtriére and the Royal Free Hospital in London were given three sets of injections, each of 3ml of PLA, 15 days apart and, for those who needed it, a fourth set of injections. Each set of injections involves 20-40 small injections into each cheek. All have been on antiretroviral therapy for more than three months, on HAART for less than three years, have plasma HIV viral load <5000 copies/mL for at least three months, and subcutaneous adipose tissue of the cheek measured by ecography <2mm.

The subjects are photographed, inspected, and their skin thickness is measured after six months, 12 months, 18 months and 24 months. Evaluation looks at quality of life as well as blood counts and changes in antiretroviral medication.

The preliminary results show no serious adverse events and measurable thickening of treated skin. Dr Aubron-Olivier said: “The high degree of satisfaction of all our patients is surely the most important result of our study.”

Newfill® : Mechanism of action



Research now underway in London

Sharon Brown from the Chelsea and Westminster Hospital, London, spoke about the randomised, open label study of PLA injections for buccal (cheek) fat pad wasting in people with HIV-related lipoatrophy. Fifteen patients in each of two arms are being given injections, one group at 0, 2 and 4 weeks; the other at 12, 14 and 16 weeks to evaluate the better time-lapse between injections. The results will be measured using facial ultrasound, photographs, visual assessments by patients and doctors, a health and depression questionnaire and blood counts. The results are due in March 2002.

New York plastic surgeon favours autologous fat transfer

New York plastic surgeon Jeff Brande, spoke to the meeting about autologous fat transfer, which is the transplantation of fat from elsewhere on the body. Dr Brande has 10 years of experience using this method as an anti-aging treatment and has been treating people with HIV-related lipoatrophy since 1996. A number of patients have been referred to him from the UK.

He said the method was to "gently tease" fat from the back or abdomen, ensuring that the fat cells remain intact, and then implant it into the face. He said the potential complications included bleeding and infections, as with any surgery, damage to veins, asymmetric irregularities and contour deformities, although he had not seen any of these. The surgery is usually performed under a general anaesthetic, although sometimes only a local anaesthetic is used. Some people suffer swelling for a week or 10 days. He said: "Patients usually want more fat."

Dr Brande showed before and after pictures of the treatment and compared them to pictures of people who had had collagen treatment including a woman who had permanent red scars. He warned people: "I would stay away from collagen if I were you." He also showed slides of people who had been treated with silicon – now illegal – that had fallen leading to sagging cheeks and buttocks, which now needed treatment. He said he now "distrusts" filler products.

Autologous fat transfer can only be performed on people with available fat elsewhere on their bodies. Dr Brande advised people: "If you have some body fat and your face is hollowing out, you should consider doing it earlier rather than later."

So-called buffalo humps, which are large accumulations of fat between the shoulder blades and on the back of the neck, are widely reported in the US, although fewer cases have been reported in the UK. Dr Brande said he sees two or three people a week with this condition. Removing the fat from a buffalo hump can involve a two hour operation, he said.

Dr Youle said he did not know of anyone who is currently offering autologous fat transfer in the UK.

Personal accounts say the pain involved in PLA treatment is well worth it

Several people spoke about their experiences of treatment with PLA. John Stevens said: "It is painful. I chose to have an anaesthetic. It is like a load of little bee stings all over the face, but I didn't care because I was so glad to have the treatment." He compared it to other painful procedures and said having a tattoo or going to the dentist involved "far worse pain". He said of the PLA injection: "It is just a tiny little prick."

"After the treatment you massage the face for 24 hours," he explained, "to make it smooth, or you can get lumps." And he added: "It is not the perfect treatment, you are not going to look 21 again, and I do not look as I did four years ago. But I am so happy I had it."

Another man told the meeting he paid £400 a session for three sessions of treatment with PLA in Harley Street. Elizabeth Laglenne commented: "That is too expensive." The speaker added that the consultant at this clinic, Odile Brennan, then treated him twice more without further charge. He said he was delighted with the results of the treatment but thought it was wrong that he had had to pay. He said it was well worth the money but it was not right that it should only be available to those who could afford £1,200.

Amanda Cameron, who works for Medi-phill, the company that distributes New-Fill, said there were 30 to 40 professionals in the UK trained to provide the treatment.

The last person to speak at the meeting was Bernard Forbes of the UK Coalition of People Living with HIV and AIDS, who urged people to take part in the campaign to persuade the NHS to offer PLA treatment. He asked people to email Georgina Strutt at Camden and Islington Health Authority saying that she should include PLA in the Londonwide Treatment Strategy that she is currently preparing. Details are on the UKC website at:

http://www.ukcoalition.org/London_Strategy/london_strategy.html

Information about New-Fill provided by Medi-phill Ltd

1. It is biocompatible and biodegradable.
2. It is immunologically inert.
3. It has no animal origin.
4. It has been used in medicine for 30 years for the encapsulation of vaccines and to carry slow-release medication

for prostate cancer and infertility.

5. It has been used in surgery for 30 years for resorbable (which means it can be broken down and assimilated into the body) orthopaedic implants, screws etc, and for resorbable sutures, as well as in skull and facial reconstructive surgery and tissue regeneration.
6. It works in two ways: a) Immediate mechanical action related to volume, and b) Delayed reaction that results in the formation of new collagen, which persists despite resorption of PLA particles.
7. It causes the proliferation of collagenous fibres that lead to natural dermal thickening.
8. The fibres make up for the absence of fat layers and the skin 'rises' back to 'normal'.
9. The skin is soft and supple.
10. It will be completely resorbed after three years.
11. The result of treatment is that of neo-tissue which progressively diminishes.
12. Repeat injections every three years are recommended by the manufacturers.

C O M M E N T

The clinician Odile Brennan and Medi-phill Ltd, distributors of New-Fill can be contacted on 020 7937 2377 or at their clinic at 40 Harley Street, W1G 9PP.

The site of New-Fill manufacturer Biotech Industry is at:

http://www.new-fill.com/Page/Anglais/sommaire.htm

Copies of a full report of the i-Base meeting can be ordered by calling 020 7407 8488 or via our website at:

http://www.i-base.org.uk

TREATMENT ACCESS

South African treatment activists defy patent laws to import generic antiretrovirals from Brazil

Graham McKerrow, HIV I-Base

A group of South African treatment activists returned home from Brazil in January carrying generic drugs for use in an AIDS treatment programme in Khayelitsha township near Cape Town The drugs smuggled from Brazil were the second shipment of Brazilian drugs and more than 50 people are already taking the Brazilian medicines in Khayelitsha.

To guarantee the quality of these drugs, an authorisation from the Medicines Control Council (MCC), the South African drug regulatory authority, was obtained prior to their use.

The activists included Joyce Pekane, Second Deputy President of the Congress of South African Trade Unions (COSATU), Zackie Achmat, Chair of the Treatment Action Campaign (TAC), and Matthew Demane, a person who is living with AIDS and currently being treated with anti-retroviral therapy (ART).

The delegates, hosted by the charity Médecins Sans Frontières (MSF), looked at Brazilian HIV/AIDS treatment programmes, visited factories that manufacture generic anti-retroviral (ARV) medicines and met government officials and people living with AIDS. The Brazilian government has formally offered the South African government help in fighting HIV/AIDS.

"In Brazil we saw what happens when a government decides to tackle HIV/AIDS. The Brazilians' decision to offer universal access to antiretroviral therapy even in the poorest areas of the country is keeping tens of thousands of people alive," said Zackie Achmat of TAC. "Central to the success of Brazil's AIDS programme is their willingness to do anything necessary to source the lowest cost quality ARVs. The South African government should pursue compulsory licensing to ensure that generic antiretrovirals can be produced and/or imported in South Africa."

The NGOs said that a court victory of the South African government against multinational pharmaceutical companies had opened the door to improved access to affordable medicines. “The South African government may need international financial help to provide treatment, but these needs will be dramatically reduced if the government takes steps to use the most affordable drugs available on the worldwide market, as the multinational pharmaceutical companies are still charging exorbitant prices for these drugs,” said Dan Mullins of Oxfam.

Despite the South African government’s refusal to provide antiretroviral treatment, three clinics run by MSF within the government primary health care centres, offer a comprehensive package of services to people living with HIV/AIDS, including antiretroviral therapy.

This project is part of an agreement between MSF and the government of the Western Cape, signed two years ago with the express intent to test the feasibility of generic antiretroviral therapy. These clinics, located in Khayelitsha, a sprawling township of 500,000 people, were opened in April 2000 and have provided treatment for opportunistic infections for more than 2,300 people living with HIV/AIDS.

In May 2001, combination ARV therapy was introduced for a group of people in advanced stages of AIDS. To date, 85 people have received ART and 50 of these are receiving Brazilian medicines. Using generic antiretrovirals offers the possibility of treating twice the number of people with the same amount of money.

“I have personally benefited from the MSF antiretroviral programme, and I have gone to Brazil to bring back generics so that more people like me can have access to these medicines,” said Matthew Damane, who is receiving ART as part of the MSF programme in Khayelitsha. “The government should publicly accept the effectiveness of these medicines and make them available to people with AIDS in South Africa.”

“Our project shows that antiretroviral therapy is feasible in a resource-poor setting, contrary to those who insist that poor Africans are not able to successfully take these drugs. Patients who were critically ill are now returning to their normal lives,” said Dr Eric Goemaere of MSF South Africa. “We have seen firsthand that these drugs can be used safely and effectively here in South Africa. As medical professionals, it is our duty to offer these benefits to as many patients as possible.”

Similar initiatives are springing up elsewhere around South Africa as medical staff become increasingly frustrated by the lack of action from their government. Nonetheless, the price of medicines continues to be a problem.

MSF has signed agreements with the Brazilian Ministry of Health (MoH) and Fiocruz, a public research body funded by the Brazilian government. The former established a cooperative agreement involving technical collaboration on the response to HIV/AIDS, so that MSF and the Brazilian MoH can collaborate to improve the delivery of treatment in resource-poor settings. The agreement with Fiocruz allows MSF to purchase antiretroviral drugs produced by FarManguinhos, the Brazilian national pharmaceutical producer, which is part of Fiocruz.

The money MSF pays will go directly into research and development of treatments for AIDS, sleeping sickness, Chagas Disease and malaria.

MSF is currently using the antiretroviral drugs AZT, 3TC, co-formulated AZT/3TC, and nevirapine produced by FarManguinhos. By using these drugs the price per patient per day falls from US$3.20 to US$1.55.

In 1996, in response to popular pressure, the Brazilian government began providing free access to antiretroviral therapy. This policy has allowed more than 100,000 people to receive ART and has reduced AIDS-related mortality by more than 50%. Between 1997 and 2000, antiretroviral treatment saved the Brazilian government $677 million it would otherwise have had to spend on hospital care and the treatment of opportunistic infections.

A COSATU statement said: “The importation of these drugs for use under strict conditions by MSF has been approved by the MCC. We are aware that it may infringe patent rights. However, we believe that, faced by an emergency caused by AIDS, and in the face of overwhelming support for the government’s view that patent rights should not be used to deny people access to life-saving medicines, this importation is in line with government and international policy.

“COSATU, TAC and MSF stand by their belief that the government and society as a whole must get antiretroviral medicines to the people who need then as quickly and cheaply as possible and must not let the vested interests of multinational pharmaceutical manufacturers prevent this. This is why these medicines are being brought in. The MSF programme in Khayelitsha is already improving the lives of more than 80 people. With affordable medicines many more people could be reached, not only in the Western Cape but throughout South Africa.”

The illegal importation is both a public relations and legal problem for the pharmaceutical companies that own the patents to the drugs. GlaxoSmithKline, which holds the patents on AZT and 3TC, will respond to infringements of its patents on a case-by-case basis, said spokesman Philip Thomson in London. The company prefers to focus on “generating greater access to medicine, and we would rather do that through partnerships than through conflict,” he said.

German-based Boehringer Ingelheim, which manufactures nevirapine, views importing a generic version of its medicine from Brazil as illegal, but has not decided how to respond, spokeswoman Judith von Gordon said.

More information is available on the websites of MSF and TAC:
www.accessmed-msf.org
http://www.tac.org.za

C O M M E N T

These activists have committed an act of defiance. By importing generic drugs from Brazil, TAC and MSF have infringed GlaxoSmithKline and Boehringer Ingelheim patents. The South African constitution protects the rights to life and dignity, and by importing these medicines, TAC and MSF believe they are upholding these rights. It is worth remembering that patent infringement is a civil matter, not a criminal one.

Because there are patents on these medicines in South Africa, there is no competition between companies to make and market these drugs in South Africa. They are therefore much too expensive. By importing these drugs from Brazil in breach of the patent law at much lower prices, TAC and MSF are challenging both the South African government and the pharmaceutical industry to take steps to allow generic drugs to be made available to those who need them

Some pharmaceutical companies have made limited offers of supplying free or cut-price drugs to certain countries under particular conditions. However, there is no doubt they could do a great deal more. They have to stop making excuses about the lack of clean water and health facilities, and tackle the issue of allowing other companies to manufacture drugs in competition to their own products so that competition will drive down prices in poor countries. The way forward is for them to set their lawyers the task of finding a way of doing this that protects the patents they hold in rich countries.

At the same time, governments must act. Prime minister Tony Blair has said he wants to lead a project to assist Africa on a scale not seen before; and chancellor Gordon Brown has already made more money available to tackle Aids in poor countries than did his predecessors here or than have his counterparts in other countries. But still far too little is being done. Even the prices of generic drugs are too high for the governments of most poor nations. Taxpayers in European nations, and North America will have to foot the bill.

ANTIRETROVIRALS

Tenofovir DF approved for marketing in European Union

Gilead Sciences Inc has announced that the European Medicines Evaluation Agency (EMEA) has granted the Marketing Authorisation for tenofovir disoproxil fumarate (Viread) in all 15 member states of the European Union. Tenofovir DF is approved in Europe for use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in patients who are experiencing early virological failure. This approval comes after the European Union's Committee for Proprietary Medicinal Products (CPMP) adopted a positive opinion on tenofovir DF in October 2001. Gilead submitted its Marketing Authorisation Application (MAA) for tenofovir DF for review by the EMEA in May 2001.

Tenofovir DF is the first nucleotide reverse transcriptase inhibitor (NtRTI) approved for the treatment of HIV. The drug works by blocking reverse transcriptase, an enzyme crucial to the replication of HIV. As a nucleotide, tenofovir DF remains in cells for longer periods of time than many other antiretroviral agents, allowing for once-daily dosing. A key benefit of tenofovir DF is its ability to reduce the viral load in HIV-1 infected adult patients who have become resistant to other available HIV drugs.

"There are increasing needs across Europe for treatments to combat HIV infection, particularly for individuals who have failed other therapy," commented Professor Brian Gazzard, Clinical Research Director, Chelsea and Westminster Hospital, Imperial College, London. "Clinical studies have highlighted tenofovir DF's safety and tolerability, favourable resistance profile and potent antiviral activity. Additionally, the drug's convenient once-daily dosing makes it an important new option for physicians and their patients with HIV infection."

At the end of 2001, an estimated 560,000 people in Western Europe were living with HIV, with 30,000 people newly infected each year. As the HIV patient population grows and patients live longer, the need for optimal long-term antiretroviral therapy has intensified.

Tenofovir DF, which is dosed as one tablet once daily with a meal, will be available shortly in Europe following completion of local reimbursement approvals. Tenofovir DF was approved for marketing in the United States by the Food and Drug Administration (FDA) on October 26, 2001. Regulatory filings for the drug also have been completed in Australia and Canada and additional regulatory filings are planned in other countries in the coming months.

Expanded Access Program

Approximately 7,700 patients with advanced HIV infection have enrolled in tenofovir DF expanded access programs in Australia, Canada, France, Germany, Ireland, Italy, the Netherlands, Portugal, Spain, the United Kingdom and the United States. More than 4,000 patients have enrolled in Europe. For more information regarding the tenofovir DF expanded access program, physicians in Europe may call +33-1-44-90-34-46, those in Australia may call 800-806-112 and those in Canada may call 1-800-GILEAD-5. These programs will continue until the product is commercially available.

NIAID funds 9-year, 6,000-participant study to look at how best to use antiretrovirals

A critical long-term study to determine which of two common HIV treatment strategies ultimately is better began in January at 21 United States locations and several sites in Australia. SMART, or Strategies for Management of Anti-Retroviral Therapies, will eventually enrol 6,000 people who will be monitored for up to nine years. The study is being conducted by the Community Programs for Clinical Research on AIDS (CPCRA), a network of community-based researchers funded by the National Institute of Allergy and Infectious Diseases (NIAID).

People with HIV and their doctors can take one of two approaches when tackling the disease. They may either suppress the virus as much as possible from the outset by continually using strong antiviral drugs or delay drug therapy until CD4+ T cells fall below a critical level.

“There is no doubt that people living with HIV/AIDS have benefited greatly from the introduction of highly active antiretroviral therapy (HAART) and other advances during the mid-1990s,” notes Anthony S Fauci MD, director of NIAID. “However, it is also undeniable that these powerful drugs cause serious side effects,” he adds. “To strike a balance between adequately aggressive treatment and minimal adverse side effects, we need hard data. SMART promises to provide just that kind of information to physicians and their patients,” Dr Fauci says.

HIV/AIDS treatment guidelines developed in the mid-1990s favoured the “hit-hard-early” strategy. In the short term, this strategy often leads to a less debilitating course of AIDS. As a result, death and disability from HIV/AIDS have declined sharply in the United States and other developed countries.

However, the drug regimens are expensive, difficult to follow and frequently cause a host of serious side effects after long-term use. Moreover, HIV may become resistant to one or more of the drugs, thereby making them ineffective. For these reasons, current HIV treatment guidelines do not recommend starting HAART as early as former guidelines did.

“There are many unanswered questions about the most appropriate use of anti-viral therapy,” says Karin Klingman MD, a medical officer in NIAID’s Division of AIDS and member of the SMART protocol team. “We simply do not know when the best time is to begin therapy after infection; when to switch from one treatment to another; or which of several key factors best predicts how the disease will progress.” It is hoped SMART will answer these questions.

SMART differs from previous AIDS treatment clinical trials in several ways. For example, although the effectiveness and toxicity of various anti-HIV therapies have been studied, this is the first study to do so over a prolonged period. SMART will compare two distinct treatment approaches and will follow enrolees for an average of seven years. In addition, while most AIDS treatment trials measure indirect indicators of AIDS development, such as the amount of virus or number of CD4+ T cells in the blood, SMART will measure clinical events such as progression to full-blown disease or to death, which take longer to occur. “The study’s length is one reason for our great emphasis on patient and physician education both prior to enrolment and throughout the study,” says Dr Klingman. SMART’s enrolment criteria are broad — teenagers as well as adults are eligible — so the findings will be applicable to as many people as possible, she adds.

In the first year, study investigators will enrol 1,000 HIV-infected people and randomly assign them to either a “go-slow” or a “hit-hard-early” treatment strategy. The hit-hard-early strategy (in which drugs are used to suppress HIV levels to low or undetectable levels) is recommended in guidelines employed by many physicians in the United States. Study participants in the go-slow arm of the study will agree not to take antiviral drugs unless their CD4+ T-cell count drops below 250 per cubic millimetre (mm3), and then they will take the drugs only until their CD4+ T-cell counts rebound above 350. The long-term feasibility of the study will be evaluated after the first year. Based on a favourable outcome, an additional 5,000 people will be enrolled over the next three years.

To take advantage of the wealth of information predicted to come from such a large and lengthy trial, the SMART study will incorporate several substudies. One, which examines treatment effects on the heart, is the first of its kind. Another will examine whether and how treatment changes body fat distribution and bone density — significant side effects of HAART — in enrolees in each group.

"Reliable evidence from randomised trials is needed to assess the risks and benefits of the strategies evaluated in SMART. The successful completion of this study will provide ground-breaking information on how to approach treatment of HIV disease," says Wafaa El-Sadr MD MPH, a principal investigator and co-chair with James Neaton PhD, of the SMART study team.

Source: NIAID Press Release. Contact information for the CPCRA units involved in the SMART trial is available at:

http://www.clinicaltrials.gov

(search term "smart"). Additional information about AIDS clinical trials and how to enrol in studies is available at the AIDS Clinical Trials Information Service (ACTIS) Web site or 1-800-874-2572 (1-800-TRIALS-A):
http://www.actis.org http://www.actis.org/

Factors associated with immunologic stability despite protease inhibitor based HAART "failure"

By Brian Boyle MD, for HIVandhepatitis.com

An accepted principle in the treatment of HIV infection is that unless the patient is on deep salvage antiretroviral therapy — when issues of viral fitness may trump the issue of complete virologic suppression — when virologic failure of an antiretroviral regimen occurs the regimen should be rapidly changed to avoid what is thought to be an inevitable immunologic failure, as well as the development of increasing viral resistance and cross-resistance to antiretrovirals.

This belief appears well founded in most HIV patients, since this is the course many will follow. However, it has been observed that some patients with incomplete viral suppression with protease inhibitor-based antiretroviral therapy — which would usually be considered virologic "failure" — do not immunologically fail, but instead continue to have stable or even rising CD4+ T cell counts.

In a clinic-based cohort study of 291 HIV-infected adults by Steven Deeks and associates, an effort was made to determine both the incidence and the risk factors of patients virologic failing protease inhibitor (PI)-based highly active antiretroviral therapy (HAART) — defined as a viral load >500 copies/mL on two consecutive occasions — returning to pre-therapy CD4+ T cell count levels. The enrolled patients' median, absolute and change in CD4+ T cell count and viral load at the time of virologic failure were 224 and +90 cells/mm3 and 3.74 and -0.94 log10 copies/mL, respectively.

The patients were observed for a median of 27.9 months. During that time, 128 stopped therapy for at least 16 weeks, 89 switched to a salvage regimen and had a successful virologic response and 47 died, with 31 of these deaths being AIDS-related.

If the data were censored to take into account patients in whom a successful salvage regimen was initiated, the median time to immunologic failure — ie a return to pretherapy CD4+ T cell levels — after the onset of virologic failure, was three years. If patient data were also censored at the time therapy was discontinued, then only 36.8% of the patients experienced immunologic failure after three years of continuous virologic failure.

Using a multivariate analysis, the change in viral load from pre-treatment baseline, and to a lesser extent the absolute level of viremia during virologic failure, were predictors of subsequent immunologic failure. The risk of immunologic failure was most likely in patients who failed to maintain viral suppression of at least 0.69 log10 copies/mL from baseline or had an absolute plasma viremia of > 4.5 log10 copies/mL. Discontinuing therapy was also associated with immunologic failure independent of viral load changes.

The authors conclude: "Immunologic failure of protease inhibitor therapy occurs among patients experiencing long-term virologic failure, but is delayed by the continued use of a partially effective antiretroviral regimen.

"Change in viral load from pre-therapy 'set point' is the single most important predictor of maintaining a CD4 cell increase. For patients with limited therapeutic options, strategies based on maintaining some degree of partial viral suppression may be warranted".

The authors note, however, that the decision is a difficult one, especially in patients with other viable treatment options, and involves the patient and clinician balancing the potential immunologic benefits of "continuing a well-tolerated regimen despite ongoing viral replication" against "the risk of continued viral evolution and the emergence of high-level drug resistance."

Ref: S Deeks et al. Duration and predictors of CD4 T-cell gains in patients who continue combination therapy despite detectable plasma viremia. *AIDS*. 2002; 16:201-207.

Hepatic injury with nevirapine related to drug level and hepatitis C infection

By Brian Boyle MD, for HIVandhepatitis.com

The potential hepatotoxicity of nevirapine (Viramune) has been well documented. As a result, nevirapine has an FDA-mandated black box warning regarding hepatotoxicity and even though severe toxicity is uncommon, clinicians have been instructed to carefully monitor their patients for this potentially fatal toxicity.

Prior studies have indicated that the acute hepatotoxicity of nevirapine arises from an acute hypersensitivity reaction, while later hepatotoxicity — which may occur in up to 20% of patients — may arise from an intrinsic hepatotoxic effect of nevirapine; however, a definitive aetiology for this toxicity has not been established.

A case-control study by González de Requena and others, published in *AIDS*, was designed to assess a possible relationship between nevirapine plasma levels and the risk of increased transaminases in individuals on nevirapine for at least four weeks. In this study, plasma nevirapine levels were measured in 70 HIV-infected patients taking nevirapine-based HAART, 33 of whom had developed transaminase elevations, and patients were stratified according to the presence of hepatitis C virus (HCV) antibodies.

The peak in transaminase levels among the 33 individuals who developed transaminitis occurred at a median time of 6.1 months after beginning nevirapine and was mild to moderate in 70% of patients. Higher nevirapine levels [OR 1.7, 95% CI 1.2-2.6, P = 0.007] and hepatitis C virus infection [OR 11.7, 95% CI 3.2-42.8, P = 0.0002] were found to be independent predictors of liver toxicity. In addition, in individuals with chronic hepatitis C, significantly elevated nevirapine levels were associated with a 92% risk of liver toxicity.

The authors conclude, “Our preliminary findings support the theory that nevirapine-associated liver toxicity occurring after several months on therapy is not part of a systemic hypersensitivity reaction, and seems to correlate with higher plasma drug concentrations involving a dose-dependent mechanism. Chronic HCV infection acts as an independent predisposing factor for the development of nevirapine-related liver toxicity. Therefore, monitoring steady-state nevirapine plasma levels, especially in patients with chronic hepatitis C, may be warranted.”

Ref: D González de Requena and others. Liver Toxicity Caused by Nevirapine. *AIDS*. 2002; 16:290-291.

Study finds that PI-containing regimens have a beneficial effect on oral candidiasis independent of any immune reconstitution

Graham McKerrow, HIV i-Base

Highly active antiretroviral therapy containing protease inhibitors (PIs) have an early beneficial effect on Candida virulence in the oral cavities, independent of any immune reconstitution, report Italian researchers.

Dr Antonio Cassone and colleagues at the department of Bacteriology and Medical Mycology of the Instituto Superiore di Sanita in Rome, say that PIs have this beneficial effect within weeks of starting treatment.

Previously Dr Cassone and colleagues had reported that some patients treated with PIs showed resolution of oral candidiasis long before any rise in the CD4+ T cell counts. The researchers hypothesised that PIs inhibited the activity of secretory aspartyl proteinase (Sap), a virulence trait for mucosal candidiasis. In the January 15 issue of the Journal of Infectious Diseases they report confirmation of this effect in a cross-sectional study of 30 therapy-naïve patients with HIV.

One group of 15 patients was treated with PI containing HAART regimens, and another group of 15 patients was treated with NNRTI HAART. The researchers tested saliva samples from all subjects on days 0, 14, 30, 90 and 180.

Of those treated with PI HAART, Sap was detected in the saliva of 11 patients at baseline and then in 6, 3, 0 and 0 at subsequent points. Of those treated with NNRTI HAART, Sap was detected in 7 patients at baseline and then in 7, 9, 6, and 5 patients at subsequent points.

In another 30 patients Sap was detected in 0 of 15 after one year on PI HAART, and it was detected in 7 of 15 subjects after a year of treatment on NNRTI HAART.

Dr Cassone and colleagues write: “The anti-Sap effect of PI HAART was associated with clinical resolution of oral candidiasis but not with late and inconstant recovery of anticandidal cellular immunity.

“In all subjects the two therapeutic regimens compared well in increasing CD4+ T cell counts and abating viraemia. Thus, PIs

exert an early, immune reconstitution-independent effect on candida virulence in the oral cavities of HIV-positive subjects."

Ref: J Infect Dis 2002;185:188-195.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd= Retrieve&db=PubMed&list_uids=11807692&dopt=Abstract

It may be important to screen and treat riboflavin deficiency in patients on nucleoside analogues

Graham McKerrow, HIV i-Base

Doctors at the Mercer University School of Medicine in Georgia, USA, recommend screening and treating HIV-infected people on nucleoside analogues for riboflavin deficiency. This follows observation that signs of mitochondrial toxicity improved with riboflavin treatment in an HIV-infected patient who developed type B lactic acidosis while receiving three nucleoside analogues.

Type B lactic acidosis is a rare and often fatal complication seen in patients receiving the nucleoside analogues zidovudine (ZDV, AZT, Retrovir), stavudine (D4T, Zerit), didanosine (ddI, Videx) and lamivudine (3TC, Epivir).

Drs Saundra D Dalton and Ali R Rahimi describe the case of a 51-year-old HIV-positive woman who had been taking lamivudine, stavudine, zidovudine and nevirapine for two years. She presented with nausea, vomiting, abdominal pain and hepatic steatosis. Signs of mitochondrial toxicity were demonstrated by diffuse myopathy and pancreatitis. Serum riboflavin levels documented a deficiency that was treated with 50mg of riboflavin daily, the doctors report in the December issue of Aids Patient Care and STDs.

Immediately after treatment, serum blood urea nitrogen level, lactic acid levels, and arterial blood pH all returned to normal values. Her signs of mitochondrial toxicity also improved after treatment with riboflavin.

The two doctors report: "Successful reversal of the patient's type B lactic acidosis after riboflavin therapy suggested that riboflavin deficiency plays a direct role in the development of nucleotide analogue-induced lactic acidosis."

They add: "It is impossible to predict which patients are predisposed to the development of this syndrome. For this reason, it may be important to screen and treat riboflavin deficiency in patients on nucleoside analogues."

Ref: AIDS Patient Care STDs 2001;15:611-614.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd= Retrieve&db=PubMed&list_uids=11788075&dopt=Abstract

METABOLIC TOXICITIES AND SIDE EFFECTS

Managing the metabolic side effects of antiretroviral therapy

Mark Mascolini, for Treatment Directory at amfAR.org

Introduction

Quick approval of antiretrovirals in the late 1990s saved lives, but at a price. The speedy development and testing of these potent drugs, in relatively small studies, gave researchers little opportunity to size up side effects. Obvious short-term problems — nausea with ritonavir and rash with nevirapine, for example — seemed a fair trade-off for the rapidly recognised clinical benefits. Only when thousands of people began taking antiretrovirals for more than a typical study's 48 weeks did today's familiar, portentous, and sometimes devastating side effects become apparent.

The emergence of lipodystrophy, hyperlipidemia, and insulin resistance, coupled with closer scrutiny of liver toxicity, high lactates, and other threats, fostered the dramatic rethinking of antiretroviral tactics that continues today. These tactics come in many guises — delayed treatment of drug-naive people, swapping one drug for another, treatment interruptions, and pulsed therapy. But all these approaches share a common feature: avoiding antiretrovirals, whether that means one drug, one class, or all of them.

Shunning anti-HIV drugs has its risks, and its benefits remain largely unproven. But so far clinical research has produced only a handful of other tools to counter side effects. Often these other tools are other medicines with their own toxicities, plus interactions with protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and nucleoside reverse transcriptase inhibitors (NRTIs or nucleoside analogues). This article surveys recent findings on managing hyperlipidemia, insulin resistance, and lipodystrophy.

Elevated blood lipids

Advanced HIV infection itself can boost triglycerides in the blood and lower levels of high-density lipoprotein cholesterol (HDL-C, or "good" cholesterol). Protease inhibitors compound these problems, hiking blood serum triglycerides, total cholesterol, and low-density lipoprotein cholesterol (LDL-C, or "bad" cholesterol).

Ritonavir raises all these lipids in HIV-negative people after only two weeks. As noted in US Department of Health and Human Services (HHS) antiretroviral guidelines, this evidence moves some experts to recommend measuring cholesterol and triglycerides before starting PIs and every three to four months afterward. People who have elevated triglyceride levels before beginning PIs, the HHS panel adds, should probably have their blood lipids measured one to two months after starting treatment. Classic heart disease risk factors should also be assessed.

What should be done with the results of these tests? Different authorities have different suggestions. The US National Cholesterol Education Program (NCEP) recommends diet and exercise for people with:

- ⇒ LDL-C at or above 100 mg/dL (if they already have heart disease and a 10-year risk above 20%)
- ⇒ LDL-C at or above 130 mg/dL (if they do not already have two or more other coronary risk factors)
- ⇒ LDL-C at or above 160 mg/dL (if they do not already have heart disease and have fewer than two other coronary risk factors)

For these three respective groups, the NCEP says "consider drug therapy" with:

- ⇒ LDL-C at or above 130 mg/dL
- ⇒ LDL-C at or above 160 mg/dL (if the 10-year heart disease risk is below 10%) or at or above 130 mg/dL (if the ten-year risk is 10% to 20%)
- ⇒ LDL-C at or above 190 mg/dL

The NCEP did not have people with HIV infection in mind when it formulated those recommendations. In its 2001 guidelines, the British HIV Association (BHIVA) issued much more specific advice for HIV-infected people:

Cholesterol repeatedly above 250 mg/dL (with LDL:HDL ratio above 4:1):

1) Switch PI to PI-sparing regimen (in people taking their first regimen)
2) Recommend dietary advice, exercise, stopping smoking, and blood pressure control
3) Pravastatin (40 mg) each night, or consider atorvastatin (10 mg) each night

LDL-C:HDL-C ratio above 4:1: as above

Fasting triglycerides repeatedly above 310 mg/dL:

1) Switch PI to PI-sparing regimen (in people taking their first regimen)
2) Recommend dietary advice, exercise, stopping smoking, and blood pressure control
3) Fenofibrate (67 to 267 mg once daily), or gemfibrozil (300 to 600 mg once daily)

Unfasted triglycerides repeatedly above 390 mg/dL: as above.

Diet and exercise

The AIDS Clinical Trials Group (ACTG) Cardiovascular Disease Focus Group recommends dietary advice and regular aerobic exercise for any HIV-infected person with a fasting triglyceride tally above 200 mg/dL. But little work has weighed the effects of diet and exercise on high lipids or on the abdominal weight gain of lipodystrophy.

One problem with prescribing diets for people taking antiretrovirals is that "the need for lipid lowering and weight gain may coexist in patients who often experience prominent gastrointestinal symptoms." The ACTG also notes that people on low-fat diets may add carbohydrates, which could raise triglycerides and lower HDL-C.

Complicating matters further, the best diet for someone with severely elevated triglycerides differs from the best diet for someone with high cholesterol. Clinicians not well versed in these matters clearly need a dietitian's help.

In one study that followed the NCEP guidelines, diet and exercise trimmed cholesterol levels by 29% (a significant drop) in eight HIV-positive people with lipid abnormalities. But diet and exercise did little to help 12 others who tried it. Dietary advice had little impact on cholesterol in a 24-week comparison of advice versus advice plus pravastatin (see "Statins, fibrates, fish oil" below).

Eighteen men who followed a program of 64 resistance-training sessions exhibited increased lean muscle mass while lowering fasting serum triglycerides from 281 to 204 mg/dL, a significant change. The authors suggested that building muscle through exercise "may promote triglyceride clearance from the circulation." A study of six men with lipodystrophy who had a ten-week course of aerobic and resistance training confirmed the significant drop in triglycerides and also logged a significant 19% decrease in total cholesterol.

Trading a PI for nevirapine or abacavir

A handful of studies, most of them not randomised, found that lipids elevated during protease inhibitor therapy fell after a switch

to nevirapine or abacavir. Substituting efavirenz for a PI does not consistently improve lipid levels. Such results inspired BHIVA's advice to try a PI-sparing combination when someone with high cholesterol or triglycerides is taking a first-line PI. Some work found a greater incidence of treatment failure when switching from a first PI to nevirapine or abacavir in people with prior NRTI therapy.

Those with NRTI exposure before taking a protease inhibitor may have HIV that has developed some resistance to those drugs. The nevirapine or triple NRTI route becomes riskier for them because of the relative ease with which further drug resistance could evolve.

Nevirapine may be the best switch option, if other research confirms the results from the Atlantic study. That trial randomised treatment-naive people to take ddI and d4T with nevirapine, indinavir, or 3TC. Participants in the 98-person lipid metabolism substudy started with cholesterol and triglyceride levels within the normal range, except that HDL-C was low. After 96 weeks, HDL-C was 40% above baseline in the nevirapine group, compared with 6% in the indinavir group and 20% in the 3TC group.

Like the other regimens, the nevirapine-containing one exhibited an increase in LDL-C levels. This somewhat mitigated nevirapine's protective effect. The total cholesterol:HDL-C ratio, considered by many to be the best predictor of heart disease, fell 6% in the nevirapine group (total cholesterol up 22%) while it rose 25% in the indinavir group (total cholesterol up 22%) and just 2% above baseline in the 3TC group (total cholesterol up 14%). Except for the HDL-C rise, the differences between nevirapine and 3TC were not statistically significant.

Statins, fibrates, fish oil

Like the BHIVA experts, the ACTG heart disease panel calls for statins in PI-treated people with high cholesterol, but not just any statins. Some of these lipid-lowering agents interact with PIs more than others due to common metabolic pathways in the liver's cytochrome P450 system. The ACTG gives the nod to pravastatin (at 20 mg daily) or atorvastatin (at 10 mg daily), with fluvastatin as an "acceptable alternative agent." (Cerivastatin, once recommended by ACTG as another alternative statin, has since been recalled by the manufacturer after reports of sometimes fatal rhabdomyolysis.) Lovastatin and simvastatin, they advise, should not be given with PIs. BHIVA also recommends pravastatin and atorvastatin as the agents of choice, but they set the pravastatin dose at 40 mg daily.

In the study that followed NCEP intervention rules, atorvastatin started at 10 mg daily cut cholesterol by 19% and triglycerides by 21% in the 10 people who took only that antilipid medication. A more recent study randomised 31 PI-treated men with cholesterol levels above 6.5 mmol/L (250 mg/dL) to get dietary advice or advice plus 40 mg of pravastatin daily for 24 weeks. Total cholesterol dwindled 17.3% in the advice-plus-pravastatin group, a significant fall, versus 4% in men who received only dietary advice. Drops in dangerous LDL-C entirely accounted for the total cholesterol decrease.

In a chart review of 77 HIV-infected people who took statins, gemfibrozil, or both for hyperlipidemia, median total cholesterol fell 13% in the statin-only group, and fasting triglycerides dropped only 5%. Both changes lacked statistical significance. A little more than half of the 29 people taking only a statin used atorvastatin, while 27% took pravastatin and 18% simvastatin. The researchers suspected poor statin adherence because lipid levels actually rose in some individuals. When they dropped these nonresponders from the analysis, triglycerides did fall significantly, but cholesterol still did not. In 55 people taking only gemfibrozil, median triglycerides fell by half, a highly significant change, and total cholesterol sank 13%. Among 17 people taking a statin plus gemfibrozil, triglycerides dropped by 36% and cholesterol by 22%.

Gemfibrozil falls into the antilipid class called fibrates, which the ACTG panel lists as "viable alternative agents" when people have high cholesterol and high triglycerides. Fibrates are the prime choice, the ACTG says, for isolated hypertriglyceridemia, advice echoed by BHIVA. The ACTG experts suggest fenofibrate may have an edge over gemfibrozil because it is easier to take and does a better job lowering LDL-C. But without further evidence, they see "no compelling reason" to pick fenofibrate over gemfibrozil.

In the NCEP-guided study, only six of 25 people reduced cholesterol and triglyceride levels with gemfibrozil alone. In the 19 people who had to add atorvastatin to gemfibrozil, average cholesterol sank by 30% and triglycerides by 60%. Combining fibrates and statins raises a risk of muscle toxicity, but these clinicians saw no myopathy (muscle wasting) in the 19 people taking the two drugs for an average 6.5 months.

A randomised, double-blind study of a low-fat diet plus either gemfibrozil or placebo in 36 men taking PIs recorded lower triglycerides in the gemfibrozil group and triglyceride gains in the diet-only group after 20 weeks. But the triglyceride drop in men taking gemfibrozil lacked statistical significance. Low-fat diet alone may have failed to lower triglycerides because half the enrolees were already following such a diet when the study began.

Fish oils, or omega-3 fatty acids, can pare high triglycerides, and the ACTG panel suggests that they "may be tried" in people with triglycerides above 1,000 mg/dL. The panel notes, though, that fish oils sometimes paradoxically boost triglycerides, that they have not been studied in people with PI-induced hypertriglyceridemia, and that high doses may abet insulin resistance in people with diabetes. Moderate doses of 1.7 g daily apparently do not promote insulin resistance.

High-dose niacin increases HDL-C to a much greater extent than the statins, which mainly act to reduce LDL-C. It also has

a number of side effects. The ACTG panel recommends staying away from niacin because it causes insulin resistance even in people without diabetes. Bile-sequestering resins like cholestyramine (Questran) and colestipol (Colestid) bind to liver bile in the intestines, causing the liver to absorb more cholesterol in order to increase bile production. The ACTG panel also advised against these agents because they can inflate triglyceride levels in the blood.

High blood glucose and insulin resistance

Insulin regulates glucose by inhibiting its production in the liver and aiding its uptake by muscle, fat, and other cells. When these mechanisms falter — a problem called insulin resistance — glucose levels climb. For people without diabetes, HHS guideline writers note that "some experts" call for fasting blood glucose measures every three to four months during the first year of PI therapy. They do not recommend routine glucose tolerance tests. People starting a PI, they add, should know the warning signs of high glucose: excessive thirst, hunger, or urination.

PI-sparing regimens and diet

Several studies implicate PIs in insulin resistance, even in people without lipodystrophy or without HIV infection. David Nolan and Simon Mallal (Royal Perth Hospital) cite studies like these in suggesting "that insulin resistance precedes, and contributes to, visceral adiposity."

Despite this evidence that PIs provoke insulin resistance, the HHS panel observes that "the reversibility [of insulin resistance and hyperglycaemia] is currently unknown due to limited data." Studies substituting an NNRTI for a PI to ease insulin resistance, the panel maintains, are "inconclusive." BHIVA experts disagree. They recommend switching to a PI-sparing regimen when symptoms of glucose irregularities appear, but only if the PI is part of a person's first antiretroviral combination. In some studies, switching from a PI to nevirapine significantly lowered glucose and insulin resistance. Insulin resistance also improved in a trial of 15 people who substituted abacavir for a PI. In 20 people who traded a PI for efavirenz, insulin resistance improved within six months of the switch. But another study in 41 people found no change in insulin resistance one year after efavirenz replaced a PI.

BHIVA also recommends dietary advice and exercise for people with glucose intolerance, but data on these interventions remain slim. A study of 62 men and 23 women with HIV infection and fat redistribution linked only three factors to high insulin levels: older age, higher polyunsaturated-to-saturated fat ratio, and longer PI use. More dietary fibre correlated with lower insulin levels. The authors suggest that polyunsaturated fats and fibre "may be important targets for dietary modification" in patients like these.

Metformin and glitazones

Metformin (Glucophage) and the glitazones (eg, Avandia) are both therapies used to reverse conventional diabetes. They both increase cellular sensitivity to insulin. High blood levels of glucose and insulin decrease as a result. The latest BHIVA guidelines offer specific treatment advice for glucose intolerance and high insulin:

All symptoms of glucose intolerance:

1) Dietary advice and exercise
2) Switch PI to PI-sparing regimen (in people taking their first regimen)

Glucose intolerance (fasting glucose 101 to 115 mg/dL or two-hour glucose tolerance test 117 to 185 mg/dL) with body mass index above 25 mg/kg2, insulin above 17 mU/L, and haemoglobin A1C above 6.5 mU/L):

1) Consider metformin (500 mg twice daily)
2) Switch off PI

Diabetes (fasting glucose above 117 mg/dL random value or two-hour glucose tolerance test above 185 mg/dL with the same additional parameters listed above):

1) Metformin (500 mg twice daily)
2) Review after three months

Body mass index 18 to 25 mg/kg2 with insulin above 17 mU/L and haemoglobin A1C above 6.5 mU/L:

1) Sulphonylurea therapy
2) Consider metformin (500 mg twice daily)

Body mass index below 18 mg/kg2 with lipoatrophy, insulin above 17 mU/L, and haemoglobin A1C above 6.5 mU/L:

1) Consider rosiglitazone (2 to 5 mg daily) or pioglitazone
2) Seek clinical opinion

Evidence supporting this advice is not overwhelming, but there is some. A randomised study of metformin versus no treatment in 27 PI-treated people with central weight gain found significant drops in fasting glucose, insulin, and triglycerides in the metformin group after two months. Visceral fat also fell. But the high dose, 850 mg three times daily, probably contributed to two study dropouts caused by severe diarrhoea and abdominal cramps. Metformin also cut subcutaneous fat in this study, so it is not the best option for people with lipoatrophy. (Note that BHIVA opts for a glitazone in people with lipoatrophy and high insulin.) Another problem with metformin in people taking antiretrovirals is that it can cause lactic acidosis, which is also a rare but dangerous side effect of NRTIs.

Other researchers studied a lower metformin dose in 26 people with lipodystrophy, 500 mg twice daily, and BHIVA adopted that dose. This three-month placebo-controlled trial charted significant drops in insulin, weight, and diastolic blood pressure in the metformin group. Those taking metformin also lost more visceral fat than those on placebo, but not significantly more. As in the high-dose metformin study, subcutaneous fat also decreased. These investigators stress that the study excluded people with a history of liver trouble, kidney failure, diabetes, or substance abuse—problems in many people with HIV infection.

Whereas metformin lowers subcutaneous fat, glitazones add fat cells. An ongoing trial, ACTG 5082, may show whether glitazones offset the subcutaneous fat wasting caused by metformin. This trial randomised people with insulin resistance and excess abdominal fat to take metformin, rosiglitazone (Avandia), or both. In a pilot study of troglitazone in six antiretroviral-treated men with diabetes, the drug improved insulin sensitivity in four of them. It also increased lean body mass and subcutaneous fat while decreasing visceral fat. A larger study of troglitazone in HIV-negative people with congenital lipodystrophy had similar results. Troglitazone (Rezulin) has been removed from the market because of liver toxicity, so researchers now focus on rosiglitazone and pioglitazone.

Fat accumulation

Making sense of studies that attempt to reverse therapy-associated increases in fat tissue (lipohypertrophy) remains a challenge for many reasons. Probably most important is the lack of a case definition for lipodystrophy, which may include various types of fat accumulation and/or fat loss (lipoatrophy). Lipohypertrophy occurs around the abdominal organs or viscera (causing truncal enlargement or abdominal paunch), between the shoulder blades (causing “buffalo hump”) and in women’s breasts. Lipoatrophy affects the subcutaneous fat layer, especially in the limbs and cheeks. Most studies lack control arms; they use different (often subjective) measures to gauge fat changes; and follow-up has generally been short. As a result, neither the HHS nor BHIVA ventures any advice on managing lipodystrophy, besides viewing with scepticism the value of switching from PIs.

Switching to a non-PI regimen

Switch studies are particularly hard to evaluate, for the reasons just mentioned. But a review of 10 switch studies at one meeting last year noted only one (involving 17 people switching to abacavir) that claimed substantial improvement in lipohypertrophy. A similar review of eight switch studies at another meeting in 2000 counted only one in which fat abnormalities improved — an update of the 17-person abacavir study.

These dismal results are not surprising. William Powderly (Washington University, St. Louis) noted that several factors may explain the failure of switching to reverse any suspected drug toxicity: the agent switched from is uninvolved or it is required for the establishment, but not the maintenance, of the abnormality; the change is irreversible; the toxicity is multifactorial; or follow-up is too short.

The HIV Outpatient Study (HOPS) made plain the multifactorial nature of lipodystrophy. Statistical analysis of factors contributing to fat gains in 104 members of a 1,077-person cohort found that treatment duration was only one of six variables that independently predicted lipohypertrophy. Among the others were age, higher body mass index (ratio of weight to height), lower pretreatment viral load, HIV viral load below the level of quantification (especially for more than two years), and haemophilia.

The Atlantic Study’s fat substudy mentioned above underscored the danger in blaming one class of antiretrovirals for fat accumulation. (Atlantic randomised treatment-naive people to take indinavir, nevirapine, or 3TC with ddI and d4T.) After a median 96 weeks of treatment, 13% taking indinavir, 10% taking nevirapine, and 23% taking 3TC had lipohypertrophy without lipoatrophy. Both hypertrophy and atrophy affected 15% on indinavir, 15% on nevirapine, and 16% on 3TC. None of the differences was statistically significant.

Such results bolster BHIVA’s advice that “individuals switching must consider that they may risk their long-term HIV management in exchange for an uncertain outcome with regard to their lipodystrophy.”

Exercise

Three published studies evaluated the effect of exercise on weight and fat in HIV-infected people without wasting. The first tried resistance training — weight lifting — four times a week for 16 weeks in 18 men. All were taking PIs, and 14 had excess central fat. Lean body mass increased significantly and the men got stronger, but they did not lose fat in the trunk, arms, or legs.

The second study combined resistance training with aerobic exercise (treadmill or stationary bike) in 10 men with abdominal weight gain, nine of whom were taking PIs. After they exercised three times weekly for 16 weeks, total body fat dropped significantly by about 2%, mostly from the trunk. Weight and lean mass did not change significantly.

A third study evaluated only aerobic exercise (on treadmills and other machines) in 54 men and eight women, many of them above ideal body weight. Half exercised three times a week for 12 weeks and the other half did not. Weight, subcutaneous fat (by skinfold thickness), central fat, and waist-to-hip ratio fell significantly among exercisers compared with controls. Waist size, which the authors call "the most robust anthropometric predictor of visceral adipose tissue," also fell significantly in the exercisers.

These findings cannot be readily applied to people with antiretroviral-related fat gains because only 14 of the 62 enrolees were taking HAART. The last person to complete the exercise program did so in 1998, and the researchers did not report any baseline abnormalities that looked like lipodystrophy. They note the need "to assess whether central fat can be preferentially reduced [by aerobic exercise]…without exaggerating the loss of peripheral fat." A possible confounding variable is a significant on-study reduction in dietary fat among the exercisers.

A smaller randomised study of 12 men with lipodystrophy compared no exercise with aerobic plus resistance training. As in the earlier aerobic/anaerobic exercise study, fat decreased significantly among the exercisers. Much of it was apparently from the midriff, since the exercisers' waist-to-hip ratio improved significantly. The authors did not directly report changes in peripheral fat, but arm and leg circumference both grew significantly in the exercise group.

Steroids, testosterone, metformin

These exercise studies excluded steroid use, which increases muscle mass. Many clinicians familiar with HIV lipodystrophy are wary of steroid toxicity. BHIVA cautions that "anabolic steroids are not suitable for treatment of lipid abnormalities, due to concerns regarding worsening lipid profiles, fat loss and potential for liver function disturbances." The effect of steroids on gonadal function remains poorly described, and is a cause for concern since many people with HIV are hypogonadal.

Twelve-week placebo-controlled studies of the steroids oxymetholone (for lipodystrophy and wasting) and nandrolone (for wasting) found that both increased lean muscle, but neither reduced fat mass. Four of 56 people quit the oxymetholone study because of liver toxicity. "Good" HDL-C dropped among people taking nandrolone, as did two hormones that reflect gonadal function.

Testosterone replacement also lowers HDL-C. BHIVA rates it "only suitable for repeatedly hypogonadal and asymptomatic men." The ACTG has mounted a placebo-controlled trial (A5079) of testosterone skin gel for men with low serum testosterone and abdominal obesity.

A double-blind, placebo-controlled trial of metformin for men with lipodystrophy recorded a significant drop in weight with metformin versus placebo and a substantial, but not statistically significant, decrease in visceral abdominal fat. Subcutaneous abdominal fat also fell in this three-month study, so the visceral-to-subcutaneous fat ratio did not change. The ACTG is studying metformin with or without rosiglitazone in people with central fat gains.

Recombinant human growth hormone

Researchers continue to search for a dose of recombinant human growth hormone (rhGH) that trims visceral fat and still proves tolerable. A meticulous study of HIV-infected men with or without excess visceral fat linked low endogenous growth hormone with visceral adiposity. In a nine-month placebo-controlled trial of rhGH in 30 abdominally obese HIV-negative men, only 1mg of the drug daily lowered visceral fat by 18%. But the lowest dose tried so far in HIV-infected people with lipodystrophy, 4mg every other day, still caused side effects.

This study involved 14 people with "truncal enlargement" who first took 6mg of rhGH daily for 24 weeks. After a 12-week break, they took a 4-mg dose for another 24 weeks. The lower dose significantly reduced visceral fat by 15%, but did not improve skeletal muscle mass or lower cholesterol. Even at this reduced dose recipients complained of pain and stiffness, and triglycerides climbed in some. Growth hormone can also increase resistance to insulin: Diabetes developed in two participants in this study, but the group had high baseline insulin levels.

Another limitation is that even at 6mg daily, growth hormone's effect on visceral fat is temporary.

Researchers at the University of California, San Francisco, are testing 1mg daily in people with HIV-related lipodystrophy. A placebo-controlled trial is evaluating 4mg every day or every other day. BHIVA advises that "there is not enough evidence for the use of growth hormone [for fat accumulation] outside of clinical trials."

Surgery

Some people with dorsocervical fat accumulation, so-called buffalo hump, have turned to surgical remedies such as liposuction. Improvements are transient, because surgery does not address potential mechanisms of fat accumulation. Patrick Amard, a Parisian surgeon treating facial atrophy (see below), believes total surgical excision of neck fat may be more effective

than liposuction, but long-term follow-up is lacking. Neither liposuction nor surgical excision is practical with visceral fat.

Fat atrophy

The large HIV Outpatient Study mentioned above also looked at the risk factors for fat loss, or atrophy. Fat loss occurred in 171 of the cohort's 1,077 members. The major identified risk factors were age, time since AIDS diagnosis, low nadir and current CD4 count, white race, and use of either d4T or indinavir.

Antiretroviral-induced fat atrophy has proved resistant to remedies except for cosmetic surgery. BHIVA experts believe "it remains unclear…whether peripheral lipoatrophy is treatable."

Switching NRTIs

Because research implicates NRTIs in this aspect of lipodystrophy, some investigators have focused on pinpointing a particular nucleoside to justify avoiding or switching from that drug. The leading suspect is d4T. Although several studies have yielded much incriminating evidence, all of it is circumstantial, and other research does not implicate d4T.

Most studies finding fault with d4T are cohort analyses, which can suggest, but not prove, cause. Many people who began to suffer lipoatrophy while taking d4T may have started with other NRTIs that failed or proved intolerable, and all of the nucleosides taken could have contributed to the problem. In four cohort studies of first-line d4T, two found a higher risk of lipoatrophy with d4T and two did not.

In another study of 39 people starting antiretrovirals with a d4T regimen and 76 starting with ZDV, rates of lipoatrophy did not differ between the groups after nearly two years. In that time, study participants did not change NRTIs.

One published trial of 29 men switching from d4T to ZDV or abacavir did chart improvements in subcutaneous abdominal and thigh fat but not in facial fat. The study was not randomised, and several people taking two NRTIs added nevirapine when they switched from d4T. Perhaps the more potent triple regimen controlled their HIV better, some suggest, so they gained weight, including peripheral fat.

A more recent study randomised 105 people with lipoatrophy to continue taking regimens containing ZDV or d4T, or to substitute abacavir for those NRTIs; 80% were taking d4T. After 24 weeks, investigators measured significant gains in subcutaneous fat in the switch group. The gains were so small, though, that neither study participants nor clinicians even noticed them. On the basis of these improvements, the researchers estimated that it would take four to five years to reverse lipoatrophy.

Reviewing some of the literature in a recent article, Judith Currier (UCLA) noted potential biases in studies pointing to d4T. She added that recent results "support earlier studies suggesting that [d4T] may be particularly implicated" in lipoatrophy.

Even if lipoatrophy occurs more often in patients taking d4T, it still occurs in patients not taking d4T. One newly published study prospectively followed 86 men and 29 women, all treatment-naive patients who started ZDV- or d4T-containing regimens and did not switch treatments. After a median 101 weeks of observation, the incidence of lipoatrophy (and any lipodystrophy) was the same with either drug.

Surgery

The BHIVA guidelines are adamant on the question of changing therapy to reverse lipoatrophy: "Switching between drugs or drug classes has not led to resolution of lipoatrophy and cannot be routinely recommended. Improvement of significant facial or peripheral limb lipoatrophy does not occur over periods of greater than six months off therapy."

Switching from d4T may owe some of its popularity to the near-total lack of other remedies for lipoatrophy. In fact, some interventions for other metabolic complications, such as metformin and aerobic exercise, can worsen subcutaneous fat loss. So people with facial atrophy have turned to a tactic that does show some promise:

Cosmetic surgery

One technique involves facial implants of fat harvested from another part of that person's body. A noncomparative, six-month study of this technique in 12 men and three women recorded a symmetric tripling of facial fat measured by MRI scans. Four of the 15 people rated the improvements "very good," nine "good," and two "light." The durability of this approach remains uncertain, and people with severe atrophy may not have enough fat for the implants.

Another technique pulls Gore-Tex strips into atrophic areas through surgical incisions. The surgery does leave scars and "some lumpiness typically is evident in the implanted areas." When the lumpiness does not fade, silicone can be injected to smooth the appearance.

The procedure that has stirred the greatest interest is subcutaneous injection of polylactic acid (PLA), marketed in Europe as New-Fill. Parisian surgeon Patrick Amard has used this technique in about 150 HIV-infected people with facial atrophy. PLA works by stimulating collagen production under the skin, but the skin surface remains soft and natural. In 33 men treated for

six to 32 months, dermal thickness measured by ultrasound increased significantly. Amard typically sees the best results after four sessions, and the only side effects he has noted are temporary swelling and bruising.

Clinician-surgeon teams in Manchester and London are studying the PLA technique in people with facial atrophy. At least six sites in the US and Mexico have offered PLA injections at prices ranging from $500 to $650 per session. In August 2001, the FDA blocked PLA imports into the US on the grounds that its sponsors had not obtained premarketing clearance to use an unapproved "device."

Anyone contemplating these procedures should consider that cosmetic surgery is a highly specialized discipline. A series of PLA shots under the skin may sound simple, but it takes an expert to get consistently good results. An HIV clinician who has watched the procedure performed warns people to "be wary of medical doctors willing to apply the treatment without the proper surgical training and skill."

This article, with all its references, is at:

http://www.amfar.org/cgi-bin/iowa/td/feature/record.html?record=55

Intensive diet and exercise regimen may help fight lipodystrophy

An "intensive" diet and exercise regimen may help lessen the effects of lipodystrophy, an abnormal body fat condition that is associated with the effects of anti-HIV medication, according to an anecdotal report published in the February issue of Clinical Infectious Diseases.

Reuters Health reports that lipodystrophy, which causes an atypical redistribution of fat in the body, can put patients at risk for atherosclerosis, diabetes and hypertension.

Dr Ronenn Roubenoff of Tufts University, Boston Massachusetts, and colleagues studied a 44-year-old HIV-positive man who experienced lipodystrophy while undergoing highly active antiretroviral therapy.

Within the first 2.5 years of HAART, the man had gained roughly 30 pounds and experienced abnormal fat redistribution, losing weight in his limbs while experiencing enlargement of the breasts and waistline.

To lower the patient's body fat and cholesterol, researchers tested a four-month regimen of diet and exercise. Three times per week the patient performed a 75-minute exercise program that combined cardiovascular work and strength training.

He also consumed at least 25 grams of dietary fibre daily and followed a diet in which 15% of his total caloric intake was derived from protein and 30% of his calories came from fat, with the remainder derived from carbohydrates.

At the end of four months, the patient had lost 14 pounds, lowered his cholesterol levels and experienced a 28% decrease in body fat. But the "most important" finding was that the man's visceral body fat — fat around the internal organs — dropped by 52%.

Dr Roubenoff explained in a Reuters Health interview that visceral body fat is most strongly associated with a person's risk for diabetes, high blood pressure and high cholesterol. Dr Roubenoff added that one year after the study, the patient, who had maintained the diet and exercise regimen outlined in the research, still retained many of the physical improvements witnessed after the first four months.

Dr Roubenoff stated that the research could help other people with HIV who are experiencing lipodystrophy, but he added that it might be difficult for patients to afford a personal trainer and a nutritionist, both of whom assisted the patient during the study.

However, he added that the results demonstrate that "lifestyle solution[s]," not just pharmaceuticals, can be a "powerful" treatment for this and many other conditions.

Source: Kaiser Daily HIV/AIDS Report. February 7, 2002.

Ref: R Roubenoff and others. Reduction of Abdominal Obesity in Lipodystrophy Associated with Human Immunodeficiency Virus Infection by Means of Diet and Exercise: Case Report and Proof of Principle. Clinical Infectious Diseases 2002; 34:390-393.

Abstract at:

http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd= Retrieve&db=PubMed&list_uids=11774087&dopt=Abstract

Avascular necrosis (AVN) may be increasingly common in HIV-infected patients

Brian Boyle MD, for HIVandhepatitis.com

Avascular necrosis (AVN), which is also known as osteonecrosis, is a condition associated with bone injury and death. This condition — which can cause significant joint pain and disability — often involves more than one joint, is frequently progressive, and in many patients necessitates joint replacement.

A high prevalence incidence of AVN has been reported in HIV-infected patients relative to the general population, and some reports have indicated that the incidence of AVN is increasing. The aetiology of this condition in HIV-infected patients remains unclear, but theories to date include that it is a complication related to HIV, an adverse effect of antiretrovirals or other medications or caused by an opportunistic infection, metabolic complication or another condition associated with HIV infection or treatment.

To assess the prevalence, incidence and aetiology of AVN in HIV-infected patients, Spanish investigators evaluated all HIV-infected patients diagnosed with AVN from 1990 to 2000 in a large clinical cohort that included 19 HIV clinics in two provinces in southeastern Spain. Cases of AVN were identified in this cohort from a retrospective chart review, and a case was defined as having AVN only if there was both a clinical and a radiographic diagnosis.

From 1990 to 2000, a total of 23 symptomatic cases of AVN were identified from the chart review. While only four cases were diagnosed before 1996, nine cases were diagnosed during the period from 1997 to 1999 and 10 cases were diagnosed in 2000. Thus, there was a marked increase in the annual incidence of AVN being diagnosed in AIDS patients, with the incidence increasing from 1997 to 2000 from 0.16% to 5.8%, respectively.

To assess aetiology, a number of factors were evaluated. Of the patients that developed AVN, 21 had previous exposure to antiretroviral drugs, 16 had been on HAART before being diagnosed with AVN, and 19 were receiving antiretroviral therapy at the time of diagnosis — with 19 on nucleoside analogue reverse transcriptase inhibitors (NRTI), 13 on a protease inhibitor (PI) and three with non-nucleoside reverse transcriptase inhibitor (NNRTI) as part of their HAART regimen.

The median time from initiation of antiretroviral therapy to the diagnosis of AVN was 24 months (range four months to 8.5 years). Seven (30%) patients had never received either a PI or NNRTI before developing AVN.

Three patients (13%) had cholesterol levels higher than 240 mg/dl, and five had triglyceride levels greater than 200 mg/dl. Only two patients had clinical features consistent with lipodystrophy at diagnosis of AVN. At least one identifiable risk factor for the development of AVN in HIV-negative individuals was found in 20 patients (86%), and in 13 patients (57%) more than one of these predisposing factors was present.

The authors conclude, “This study confirmed that AVN is an emerging complication of HIV infection. In the year 2000, the incidence reached a high of 1.19 cases per 1,000 patients, which is 29-fold higher than the population-based incidence. An increasing trend in the incidence of new cases of AVN in HIV-infected patients has also been observed in some institutions in the USA, and a staggeringly high prevalence of asymptomatic AVN of the hip has recently been reported.

In the present study, the sharp increase in the frequency of AVN was observed since 1997, soon after PIs were released in Spain and HAART became the standard of care for HIV-infected patients. However, HAART cannot be the only explanation for AVN because 30% of our cases had not received HAART.

Furthermore, our series do not suggest that either hyperlipidaemia or lipodystrophy are linked to AVN. In fact, only two of our patients had concurrent lipodystrophy, and although seven others had mild hypercholesterolaemia or hypertriglyceridaemia, none of them had marked hyperlipidaemia.”

Readers should note that while this study certainly indicates that more cases of AVN are being diagnosed, there are many explanations for this besides a true increase including heightened physician awareness and increased patient survival. Until we have more information (and possibly prospective studies), assessing relative incidence and aetiology remain difficult.

Clearly, however, AVN is a significant problem in HIV-infected patients and physicians who care for those patients should be on the lookout for signs or symptoms that suggest it.

Ref: F Gutiérrez and others. Avascular necrosis of the bone in HIV-infected patients: incidence and associated factors. AIDS 2002; 16:481-483.

Rheumatological complications associated with the use of indinavir and other protease inhibitors

Graham McKerrow, HIV i-Base

Doctors in Belgium report several cases of rheumatological disorders that seem to be associated with the use of the protease inhibitor indinavir. The complaints only disappeared completely when indinavir was replaced with the non-nucleoside analogue nevirapine.

Dr R Colebunders and colleagues at the Department of Clinical Sciences at the Institute of Tropical Medicine at Antwerp, Belgium, report the four cases in the January issue of the Annals of Rheumatic Diseases. Their survey, using an anonymous questionnaire of 878 people with HIV infection and treated with antiretroviral drugs, found cases of temporomandibular (the hinge of the lower jaw) dysfunction, frozen shoulder, Dupuytren's disease of the hand, and tendonitis. The researchers write that "other protease inhibitors may also cause arthralgia".

Dr Colebunders and colleagues believe this is the first report of an association between treatment with protease inhibitors and temporomandibular dysfunction.

Of the 878 patients surveyed, 674 had been treated with PIs, for an average of 15 months. Arthralgia was reported more often by patients who were on regimens containing PIs than by those on regimens that did not contain PIs, 35.5% and 26% respectively. Multivariate analysis showed arthalgia to be "highly associated" with the use of indinavir and the ritonavir-saquinavir combination.

Dr Colebunders and colleagues recommend that when patients with HIV who are being treated with protease inhibitors develop rheumatological problems, a "temporary interruption of the protease inhibitor" and its replacement by another class of ARV should be considered to prove causality.

Ref: Ann Rheum Dis 2002;61:82-84.
http://www.ncbi.nlm.nih.gov:80/entrezquery.fcgi?cmd=Retrieve&db= PubMed&listuids=11779768&dopt=Abstract

PATHOPHYSIOLOGY

Reseeding of viral reservoirs may explain poor response to HAART interruption

Faith Reidenbach, for HIVandhepatitis.com

The poor response of patients with chronic HIV infection to supervised treatment interruption, compared with responses in acutely infected patients, may be due to the emergence of different viral variants with each interruption, according to study results published in the Journal of Virology for February.

Dr Simon D Frost, of the University of California at San Diego, and colleagues formed their hypothesis after analysing data from a study conducted in Spain, which involved 12 HIV-1-infected patients who had at least a two-year history of viral suppression during highly active antiretroviral therapy. The patients stopped treatment for up to 30 days, then resumed it for 90 days, for four cycles.

The researchers measured viral load very frequently, at a median interval of two days. They say that because of this and their development of a novel Bayesian model, they were able to "obtain good estimates of the viral growth rate, the time for virus to rebound to detectable levels, and residual error even when there are many viral load measurements below the limit of detection."

Overall, the level of circulating CD4+ T cells did not decrease between the first and fourth treatment interruptions. There was a significant decrease, by about half, in the average viral reproductive rate over the course of the four cycles, with extensive between-patient variation. Still, the research team says, the average time between treatment interruption and viral rebound was approximately the same in the first and fourth interruptions.

"One possible explanation for this discrepancy is that the growth rates above and below the limit of detection were the same, but the viral load present at the beginning of the interruption increased over successive structured treatment interruption cycles," the authors suggest.

"An increase in the viral load present prior to interruption could be due to the reseeding of viral reservoirs," they continue. "Any new drug resistance mutations that emerge during treatment interruptions may be archived in these reservoirs, which could

lead to the rapid emergence of a resistant viral population in response to subsequent treatment."

"This may boost the immune response less than repeated exposure to the same viral antigens," Dr Frost pointed out in an interview with Reuters Health. "We are currently studying how the virus evolves during therapy interruption."

Based on these and other findings, Dr Frost's group draws three conclusions about the dynamics of viral replication during treatment interruption: "Multiple, short interruptions may be desirable to reduce exposure to drug, while minimizing the risk of viral rebound; a single, long interruption may be required to allow sufficient replication for the reversion of resistant virus to wild type; and multiple interruptions of intermediate length may be required to allow sufficient rebound of virus to stimulate immune responses, while minimizing the risk of damage to the CD4+ compartment."

"Given that therapy interruption is also associated with risks — letting the virus replicate can result in drops in CD4+ count and increases the chance that drug resistance will emerge — it is important to emphasize that treatment interruptions remain an experimental regimen," Dr Frost cautioned.

Ref: Frost SD, Martinez-Picado J, Ruiz L et al. Viral dynamics during structured treatment interruptions of chronic human immunodeficiency virus type 1 infection. J Virol 2002; 76:968-979.

Abstract at:
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db= PubMed&list_uids=11773372&dopt=Abstract

OTHER NEWS

Smoking damages quality of life for people with HIV, says study

Graham McKerrow, HIV I-Base

Smokers in a San Francisco study of HIV-positive patients, report poorer health-related quality of life (HRQL) than non-smokers.

Smoking was associated with a range of problems including lower general health perception, physical functions, bodily pain and energy, according to the research by Dr Margaret Chesney and colleagues from the University of California at San Francisco. They collected data for 585 HIV-positive homosexual/bisexual men, injection drug users, and their female partners who participated in the multi-centre Pulmonary Complications of HIV Infection Study.

They made a cross-sectional assessment of HRQL using the Medical Outcomes Survey Scale adapted for patients with HIV. Multivariate analysis was used to determine the impact on HRQL of smoking, CD4 loss, AIDS diagnosis, number of symptoms, study site, education, injection drug use, sex and age.

In the December 2001 issue of *AIDS Patient Care and STDs*, the researchers write: "Current smoking was independently associated with lower scores for general health perception, physical functioning, bodily pain, energy, role functioning and cognitive functioning.

"We conclude that patients with HIV infection who smoke have poorer HRQL than non-smokers. These results support the use of smoking cessation strategies for HIV infected persons who smoke cigarettes."

Ref: AIDS Patient Care and STDs 2001;15:615-624.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11788076&dopt=Abstract

Nutritional supplements can help patients gain weight, raise CD4 counts

Michael Greer, Senior Medical Writer for AIDSWEEKLY Plus

Nutritional supplements enriched with peptides and some fatty acids can help HIV patients gain weight while improving immune function, researchers in Spain report.

"Dietary counselling and intervention based on application of conventional criteria have been ineffective in preventing the progressive weight loss associated with HIV infection," according to Dr DA de Luis Roman and colleagues at Rio Hortega University Hospital in Valladolid.

A formula with high levels of n-3 fatty acids reversed HIV related weight loss and significantly raised CD4+ T cell levels, de Luis Roman and colleagues found.

They compared the benefits provided by standard enteral nutritional formulas with those of an enterotropic, peptide-based formula rich in n-3 fatty acids, according to their report. These fatty acids are known to improve coronary function and are thought to play a role in cognitive development as well.

Both standard and enriched supplements produced significant weight gains of roughly 3%, mostly in the form of increased fat mass. The peptide-based formula also produced a significant and persistent increase in CD4+ T cell counts, which was not seen after treatment with conventional formula, study data showed.

Patients who received the enriched formula were also less likely to contract infections requiring hospitalisation although the difference between groups was not statistically significant.

“Oral nutritional supplements for a three-month period were well tolerated and resulted in body weight gain in HIV-infected patients,” de Luis Roman and colleagues concluded. “Supplement-enriched formula, with peptides and n-3 fatty acids, increased CD4 count.”

The corresponding author for this report is Dr DA de Luis Roman, Endocrinologia y Nutricion, Director Ejecutivo IEN, Facultad de Medicina, H Universitario Rio Hortega, Caamano 51 bis, 3C, Valladolid 47013, Spain. E-mail: ddlr@pulso.com

Ref: de Luis Roman DA et al. Nutritional treatment for acquired immunodeficiency virus infection using an enterotropic peptide-based formula enriched with n-3 fatty acids: A randomised prospective trial, Eur J Clin Nutr 2001 Dec;55(12):1048-52.

HIV-like virus detected in wild chimpanzee

“To find this virus for the first time in the wild opens a window of opportunity to begin to study the natural transmissibility of these types of viruses in their natural host,” said investigator George M Shaw of the Howard Hughes Medical Institute.

An international team of researchers has identified a wild chimpanzee infected with simian immunodeficiency virus (SIVcpz). The identification of the infected animal strengthens the scientific case that wild chimpanzees are the reservoir of SIVcpz, which researchers believe is a relative of the human immunodeficiency virus (HIV).

The research team, which includes George M Shaw and senior author Beatrice H Hahn, reported the discovery in the January 18, 2002, issue of the journal *Science.* Shaw and Hahn are both at the University of Alabama at Birmingham, USA.

In 1999, Hahn, Shaw and their colleagues first reported evidence that human HIV-1 most likely arose because of transmission of SIVcpz from the chimpanzee, *Pan troglodytes troglodytes,* to humans. Their conclusion was based on evidence indicating that six captive chimpanzees were infected with SIVcpz.

“Since thousands of captive chimpanzees throughout the world had been screened, and only those six had been found to be positive for SIVcpz, people questioned how the chimpanzee could be the reservoir if all these other animals were negative,” said Shaw. “The reason we deduced that the chimpanzee was the source was that others considered the animals as all being equivalent. But there are four different subspecies, and we provided evidence that it was *Pan troglodytes troglodytes* native to west central Africa that was the original source of the disease. However, until now, there had been no evidence for a natural reservoir of SIVcpz in the wild.”

In the latest studies, Hahn, Shaw and their colleagues analysed urine and faecal samples from 58 animals. The animals included those of the subspecies *Pan troglodytes verus* from the Tai Forest in the Côte d’Ivoire in West Africa, and those of the subspecies *Pan troglodytes schweinfurthii* in the east African Kibale National Park in Uganda, and Gombe Stream National Park in Tanzania. The development of a highly sensitive immunological assay to test urine and faecal samples for antibodies to the virus was critical to the study’s success. This noninvasive test, developed by first author Mario L Santiago, allowed the scientists to avoid having to capture the endangered animals to take blood samples.

Of the tested animals only one — a sexually active *Pan troglodytes schweinfurthii* male from the Gombe National Park — was found to harbour SIVcpz. In order to protect the animal, the scientists are declining to reveal its identity.

Detailed analysis of the SIVcpz strain found in the Gombe chimpanzee revealed that it was different from any previously known SIVcpz or HIV-1 strains. The closest relative was a virus found in a captive *Pan troglodytes schweinfurthii* animal. According to the scientists, the lack of resemblance to other strains of the virus found in the wild animal ruled out east African chimpanzees as the natural source of human HIV.

“When we did our earlier work, we reasoned that since the virus from *schweinfurthii* was the most divergent from HIV, it must be that the human AIDS virus came from the *troglodytes* subspecies,” said Shaw. “And sure enough, when we studied the virus from *troglodytes* animals, it did resemble HIV-1.”

According to Shaw, the discovery of the virus in only one animal is not surprising, given the habitat destruction and decimation of chimpanzee populations throughout Africa. Hahn, Shaw and their colleagues are continuing to gather and analyse samples,

especially from Gombe, to see if they can detect the virus in additional animals. These studies, he said, could offer new insights into SIV that will apply to HIV.

"To find this virus for the first time in the wild opens a window of opportunity to begin to study the natural transmissibility of these types of viruses in their natural host," he said. "We also believe it may be important ultimately to understand the implications of the cross-species transmission that brought about the HIV pandemic," he said. "Is there another vector besides transmission via blood that we haven't discovered? We don't think so, but we don't know for sure."

Primatologist Jane Goodall, a co-author of the *Science* paper, and her colleagues, have studied the Gombe animals extensively. "The infected animal was born in Gombe, and they have studied it for 20 years," she said. "They know all its sexual mates and its history of sexual activity. So, we can analyse samples from those mates and their offspring and begin to understand how this virus perpetuates itself in the wild. From such studies could come clues to why the disease is benign in chimpanzees but virulent in humans," she said. "For whatever reason, SIVcpz has adapted over tens of thousands of years to the chimpanzee, so that it is less pathogenic and therefore preserves itself in its host."

"Importantly, we can also explore how SIVcpz in *troglodytes* animals differs from that in *schweinfurthii* animals," she said. Detailed comparative molecular analysis of the infectious mechanisms and pathogenicity of the different strains of SIVcpz and HIV could yield insights that will aid development of AIDS vaccines and antiviral drugs, said Shaw.

Source: Press Release Howard Hughes Medical Institute

Ref: Beatrice H Hahn, George M Shaw, Paul M Sharp et al. SIVcpz in wild chimpanzees, Science 2002 January 18; 295: 465 (in Brevia)
http://www.sciencemag.org/cgi/content/full/295/5554/465/DC1

ON THE WEB

Immune restoration: repairing the damage

ACRIA Update, Vol. 11, No. 1, Winter 2001/2002

Richard Jefferys

The ability of Highly Active Antiretroviral Therapy (HAART) to suppress HIV replication, increase CD4 cell counts in the blood, and prevent or delay opportunistic infections is now well documented. Individual responses can vary, toxicities remain a problem and the best time to start HAART continues to be debated, but the overall trend of restored immunity and prevention of illness has come as a welcome surprise.

Many researchers feared that the damage to the immune system caused by HIV would be irreversible, but HAART studies have contradicted this assumption. These studies paint a picture of immune restoration occurring in multiple phases — some fast and others slow and variable — ultimately leading to near-normal immune system function in many individuals.

Research into immune restoration also provides a new opportunity to understand the mechanisms by which HIV damages the immune system, a necessary step for designing therapies that might speed immune recovery or help people whose immunity remains impaired despite HAART.

http://ww2.aegis.org/pubs/cria/2001/CR110108.html

The immune system: behind the scenes

ACRIA Update, Vol. 11, No. 1, Winter 2001/2002

Richard Jefferys

The human immune system is a dazzlingly complicated mix of many different cells, tissues and chemical factors that work together to try to maintain health.

The immune system has evolved over billions of years to accomplish a multitude of tasks, including responding to infections but also tolerating substances — like pollen and food ingredients — that pose no danger to the body. The system, as we know, is not perfect.

Allergies represent a potentially dangerous overreaction to things that are ordinarily harmless, while weak or ineffective responses to harmful infections can lead to disease. The mounting of an immune response can be thought of as a major production, involving a vast cast of characters and a rough script to guide communications between them. The production often progresses seamlessly, but at other times, missed cues and forgotten lines may spell disaster.

http://ww2.aegis.org/pubs/cria/2001/CR110107.html

Wondering aloud: theories of one (quasi) LTNP

ACRIA Update, Vol. 11, No. 1, Winter 2001/2002

Mark Milano

Speculation abounds as to what makes a long-term non-progressor (LTNP), as do definitions of exactly what an LTNP is. Some have looked at the maintenance of HIV-specific CD4+ T cells, others at cytokines like IL-10 and still others hope to create LTNPs by using therapeutic vaccines.

In my own case, I've wondered for years if I may have stumbled on a way to slow disease progression by the use of a simple, cheap and non-intuitive treatment.

http://ww2.aegis.org/pubs/cria/2001/CR110104.html

IL-2: promiscuous cytokine or steady date

ACRIA Update, Vol. 11, No. 1, Winter 2001/2002

Tracy Swan

Interleukin-2 (IL-2) is the immune-based therapy that has been most extensively studied in HIV.

Many people continue to be intrigued by its potential, yet questions about IL-2 remain unanswered, including the most basic one — is it an effective HIV therapy? IL-2 has also been called an immune booster, an immune modulator and T-cell growth factor.

A man-made form of IL-2 was first developed in the early 1980s as a treatment for certain cancers. Although IL-2 has been studied in people with HIV since the 1980s, it hasn't been approved as a treatment for HIV disease.

http://ww2.aegis.org/pubs/cria/2001/CR110103.html

Immune-based therapies for HIV: a history

ACRIA Update, Vol. 11, No. 1, Winter 2001/2002

Richard Jefferys

The discovery of HIV in the mid-1980s led to an intensive search for therapies that might inhibit the virus's life cycle, a search that eventually produced the 16 antiretroviral drugs that are on the market today.

Finding treatments that might work by improving the function of the immune system — immune-based therapies (or IBTs) — has proved to be a more daunting task, mainly because the mechanisms by which HIV impairs immunity are still not fully understood. Without that understanding, IBTs have largely been shots in the dark, with some aiming to improve overall immune function (and thus prevent or delay opportunistic infections), and others attempting to specifically improve the immune response to HIV.

Over the years, many approaches have been proposed and studied, sometimes to great fanfare, but all have so far failed to demonstrate any measurable health benefit. As yet, there are no IBTs approved for the treatment of HIV infection or AIDS.

http://ww2.aegis.org/pubs/cria/2001/CR110102.html

Therapeutic immunisation: a vaccine by any other name

ACRIA Update, Vol. 11, No. 1, Winter 2001/2002

Jeff Gustavson

As the smoke of hope dissipates for eradication of HIV from the human body and the limitations of antiretroviral medications become all too apparent, efforts are being renewed to examine a role for immune-based interventions to help control HIV infection and potentially reduce ongoing exposure to antiretroviral medications. One way of intervening is to take vaccines that were originally designed to prevent infection and give them to people who are already infected with HIV. Strictly speaking, this is called a therapeutic immunisation.

Although other methods of stimulating the immune system are also being considered, therapeutic immunisation is likely to be less expensive and more easily tolerated than other immune boosting therapies. Despite healthy scepticism of how useful they'll be, many researchers as well as HIV positive persons are enthusiastic about their promise.

http://ww2.aegis.org/pubs/cria/2001/CR110105.html

The role of IL-10 in long-term non-progressors

ACRIA Update, Vol. 11, No. 1, Winter 2001/2002

Sean R Hosein

After becoming HIV-positive, most people usually remain physically well for years. During this time, despite outward appearances, HIV is constantly attacking the immune system. As the damage from HIV builds up, levels of important immune cells called CD4+ T cells gradually decline. Eventually the body is unable to repair the damaged immune system, leading to an AIDS diagnosis. This decline in the immune system is called disease progression.

It is noteworthy that a small proportion of people have a very different response to HIV — one that is found in only about 1% of HIV positive people. Researchers have found that this minority has relatively high and stable CD4+ T cells, low amounts of HIV in the blood, and no symptoms of HIV-related disease for prolonged periods. These people are not taking anti-HIV therapy and are called long-term non-progressors (LTNPs).

There may be several reasons that some people with HIV become LTNPs. Some are simply lucky to be born with immune cells that are difficult for HIV to enter and infect. Others may be infected with a relatively weak form of HIV. Yet research is accumulating that suggests that a vigorous immune response against HIV may play a role in helping to keep LTNPs healthy. If this immune response could be understood, perhaps better therapies against HIV could be developed.

http://ww2.aegis.org/pubs/cria/2001/CR110106.html

Antiretroviral resistance mutations chart updates

Antiretroviral Resistance Mutations, A collaborative effort of the IAS-USA Resistance Testing Panel and HIV InSite, updated 12/01.

http://hivinsite.ucsf.edu/InSite.jsp?page=md-00-00&doc=ias.usa.mutations

The Body launches major new feature section on HIV+ women

“Features at The Body: Women & HIV,” the maiden voyage of The Body’s outstanding new features area, has been launched. This comprehensive, in-depth look at HIV/AIDS among US women includes interviews with top AIDS specialists treating women, moving profiles of positive women, important resources and an online museum featuring the artworks of Visual AIDS’ female members. Throughout the year we will publish new feature sections, each focusing on an important issue in HIV/AIDS. Check it out!

http://www.thebody.com/features/women

Informative question-and-answer sessions with eight of the most prominent doctors treating HIV-positive women, including a discussion of unique side effects and treatment struggles among women.

http://www.thebody.com/features/women/docop1.html

Interviews with women from a wide range of backgrounds and ages (from 15 to 66) who are battling HIV in their bodies, in their communities and across the country.

http://www.thebody.com/features/women/profiles.html

An online gallery featuring female members of Visual AIDS, an organization devoted to promoting and preserving the creative works of HIV-positive artists.

http://www.thebody.com/features/women/visualaids/visualaids.html

A detailed listing of service organisations, books and web sites for HIV-positive women.

http://www.thebody.com/features/women/resources.html

Conference coverage of the 41st ICAAC: Post-meeting reviews

Newly available: the following post-meeting reviews, certified for CME: -

Antiretroviral Treatment: Use Available Drugs Judiciously, William A O’Brien MD, MS

Pharmacokinetics and Pharmacogenomics: Advancing Understanding One Step at a Time, Stephen Becker MD

Update on HIV-1 Drug Resistance, Daniel Kuritzkes MD

HAART Failure: The Lingering Threat of Opportunistic Infections, Henry Masur MD

Waiting in the Wings: Update on Investigational Antiretrovirals, Mike Youle MB, ChB

http://www.medscape.com/viewprogram/822?srcmp=aids-020502

Update on the management of HIV and hepatitis C virus coinfection

Marion G Peters MD, and her colleagues discuss recent developments of practical relevance to physicians who care for HIV/HCV-treated patients.

The management of HIV and hepatitis C virus (HCV) coinfection is evolving rapidly. Coinfected patients present a special challenge in the era of highly active antiretroviral therapy (HAART) because concomitant hepatotoxicity, steatosis, and cytopenias may render patients ineligible for standard therapies for HCV. Elimination of HCV is considered the "gold standard" for sustained virologic response; other important goals of anti-HCV therapy are to improve symptoms, ameliorate inflammation, decrease or reverse fibrosis, and prevent the development of hepatocellular carcinoma and liver failure.

Medscape HIV/AIDS eJournal 8(1) 2002

Full text at:

http://hiv.medscape.com/viewarticle/420681?srcmp=aids-020502

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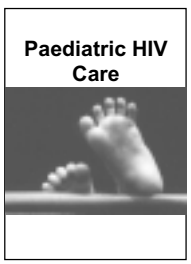

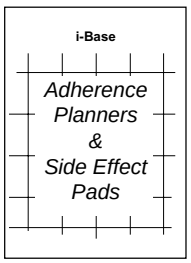

*NEW Guide To Avoiding and Managing Side Effects *(August 2001 edition)*

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*NEW Introduction to Combination Therapy *(December 2001 edition)*

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Changing Treatment - Guide to Second-line and Salvage Therapy *(July 2001 edition)*

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