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EDITORIAL

As this issue of HTB went to press the 10th Conference on Retroviruses and Opportunistic Infections (CROI) was just coming to a close. As expected, this meeting included new studies on a wide range of scientific and medical aspects of HIV research.

Full reports on new agents, antiretroviral strategy, gender and paediatric studies, generics and treatment in resource poor countries, metabolic side effects and lipodystrophy research will be covered in full in the next issue.

Even at this highly medical conference, treatment access issues are now integrated in the programme with sessions focused on both the medical and political challenges in resource poor countries. The opening ceremony included a performance by an HIV-positive choir from South Africa called Sinikithema (We Give Hope). One of the singers also spoke movingly about her own recovery from AIDS after accessing a trial of combination therapy, and also about the importance and practicality of treatment for the majority of the current 40-odd million people to whom it is currently denied. Former President Clinton also spoke about the global response. These and other presentations from the conference can be viewed over the internet as a webcast.

HTB continues to focus on treatment access, and in this issue Graham McKerrow discusses the impact of the political and financial influence of the US. It is encouraging to be able to report further pharmaceutical initiatives.

Important treatment news includes recently published studies small showing the possible importance of 4-drug therapy in some patients and that the complexity of d4T and AZT cross resistance is still underestimated – together with more interesting studies on lipodystrophy, metabolic and bone mineral changes.

'On the web' articles include links to some of the most interesting articles published by other medical sites and community journals over the last month, together with important reference items such as past conference abstracts, newly published guidelines and other related articles and on-line resources.

On a final note, we distributed an HTB survey with the last issue, and your feedback is both essential and appreciated. Thank you to everyone who has so far replied. Please, if you still have the survey around, and can find five minutes to post it back in the pre-paid envelope… we'd be very grateful. An electronic format of the survey is still available, of course, on the website...

CONFERENCE REPORT

10th Conference on Retroviruses and Opportunistic Infections
8-14th February, 2002 Boston, USA

The 10th Conference on Retroviruses and Opportunistic Infections was held from 10 – 14 February, as this issue of HTB was going to press. Attended by almost 4000 delgates and presenting over 900 pieces of research, this conference is one of the most important scientific HIV meetings.

Abstracts for the meeting are now online and can be downloaded as a fully searchable pdf file.

Symposium lectures from the meeting are also posted on the conference website and can be viewed with slides as part of the webcast facility.

http://www.retroconference.org/2003/

Early daily coverage is available at the following websites:

http://www.thebody.com/confs/retro2003/retro2003.html

http://www.hivandhepatitis.com/hiv_aids.html

http://www.natap.org

http://www.medscape.com/hiv-aidshome

Medscape requires a one time free registration.

Full reports from the conference will be in the next issue of HTB.

TREATMENT ACCESS

Bush plans $15 billion budget to treat two million people and prevent seven million infections in 14 countries – but meets criticism from activists

Graham McKerrow, HIV i-Base

President George Bush took the AIDS community by surprise at the end of January when he used his annual State of the Union address to say he would ask the US Congress to treble overseas spending on AIDS from $5 billion to $15 billion.

The White House explained that the new money would be targeted at 14 African and Caribbean countries with the intention of treating two million people with antiretroviral drugs, prevent seven million new infections – 60% of projected new infections in the 14 countries – and care for 10 million positive people and AIDS orphans.

The plan astonished observers and drew immediate criticism from some AIDS activists because it is limited to only certain countries and most of the money will bypass the Global Fund to Fight AIDS, TB and Malaria, which many people believe should be the main vehicle for funding the response to the pandemic. The Global Fund is struggling to raise money.

Mr Bush said: "Anti-retroviral drugs can extend life for many years. And the cost of those drugs has dropped from $12,000 a year to under $300 a year - which places a tremendous possibility within our grasp.

"I propose the Emergency Plan for AIDS Relief - a work of mercy beyond all current international efforts to help the people of Africa. This comprehensive plan will prevent seven million new AIDS infections, treat at least two million people with life-extending drugs, and provide humane care for millions of people suffering from AIDS, and for children orphaned by AIDS."

At a White House ceremony a few days after his address, Mr Bush expressed support for the Global Fund. However, the $15 billion, five-year plan will see less money being given annually by the US to the Global Fund; down from $380 million this year to $200 million a year for the next five years. The Global Fund "is being starved under the president's proposal," said Asia Russell of the Philadelphia-based Global Access Project.

The US seemed to indicate support for the Global Fund when Tommy Thompson, the US Secretary of Health and Human Services, was elected chairman of the Fund. Bush tried to counter criticism by saying, in February: "I've been asked whether or not we're committed to the Global AIDS Fund. Well, first of all I wouldn't put Tommy [Thompson] as the head of it if we weren't."

And the president continued: "It's more than money we bring. We bring expertise and compassion and love and the desire to develop a comprehensive system… for diagnosis and treatment and prevention."

Jeffrey Sachs, director of Columbia University's Earth Institute and an economic advisor to UN general secretary Kofi Annan, called the appointment of Mr Thompson to head the Global Fund "bizarre" and said the Bush policy seemed to be saying "if American money was going to go for something, it needed to be under American control".

Stephen Lewis, the UN envoy for AIDS in Africa, welcomed the new money saying it was "a dramatic signal from the US administration that it is ready to confront the pandemic." He told the New York Times that other wealthy countries should follow the American example.

"My prayer is that when this funding comes, we'll see a reduction of people being affected by AIDS," said Prega Ramsany, the executive director of the Southern African Development Community, which represents most countries in the region.

In Botswana, officials said they hoped the money would be used to buy drugs and to hire doctors and nurses. Botswana is the only country in Africa to commit to providing ARVs to all its citizens. But HIV is killing Botswana's medical staff. "This news is a very encouraging thing to us in Africa," commented Abinel Whendero, the acting coordinator of the government's National Aids Coordinating Agency.

Some activists criticised Mr Bush's use of language in his State of the Union address in which he referred to "AIDS victims", the "AIDS virus" and "innocent people". These are inaccurate and value-loaded terms, said Omololu Falobi of Nigeria, which disempower people and imply a hierarchy of guilt.

In the same week as the State of the Union address, Mr Bush announced that he would ask Congress to approve the spending of $16 billion on domestic US HIV treatment and prevention for the year 2004, an increase of 7% on this year. The proposals include a $93 million increase in research spending and an extra $100 million to provide antiretroviral drugs to uninsured and underinsured Americans with HIV.

The countries that will be targeted by President Bush's Emergency Plan for AIDS Relief are: Botswana, Cote d'Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda and Zambia. The $15 billion will be spread over five years, starting with $2 billion in 2004 and increasing annually.

Global Fund awards $866 million to projects in 60 countries

At the same time as the announcements in Washington about overseas and domestic spending on the response to AIDS, the Global Fund announced from its Geneva offices a series of grants amounting to $866 million over two years to projects tackling AIDS, TB and malaria.

About 60% of the new money will be used to combat HIV, including antiretroviral treatment for 500,000 people in developing countries as well as care and support for 500,000 AIDS orphans and vulnerable children. The funding will also expand prevention programmes especially among young people, and step up prevention of mother to child transmission, and voluntary counselling and testing.

Global Fund money is also being provided to combat malaria by providing 30 million African families with treated mosquito nets, and by purchasing more than four million courses of treatment of new and more effective medicines for people in Africa with resistant strains of malaria. The grants will also treat two million people with TB over the next five years.About 60% of the new money will go to Africa, with the largest amount, $93.3 million, paying for projects combating AIDS and malaria in Ethiopia. TB and AIDS programmes in India will receive $38.8 million.

This second round of grants awarded by the Global Fund brings the total disbursed and promised by the fund in 2003 and 2004 to $1.5 billion. If they meet performance standards the recipient projects could be entitled to up to another $2.4 billion after 2004. The Fund currently lacks the money to make a third round of grants scheduled for October. It estimates that at least $6.3 billion in additional contributions is needed over the next two years.

Global Fund Observer email newsletter and forum

Aidspan has launched Global Fund Observer (GFO), a two-pronged venture consisting of an e-mail-based newsletter and a related discussion forum, which will serve as an independent source for news, analysis and commentary about to the Global Fund to Fight AIDS, TB and Malaria. Both the newsletter and forum are available to subscribers at no charge.

Aidspan said in a statement that the newsletter strongly supports the Global Fund's principles but is free to critique how the fund implements its principles because the newsletter is not connected with and does not accept money from it.

To subscribe to the GFO newsletter, send an email to <receive-gfo-wsletter@aidspan.org>. Subject line and text can be left blank. To subscribe to the GFO discussion forum, send an email to <join-gfo-forum@aidspan.org>. Subscriber names and e-mail addresses will not be passed to anyone outside Aidspan.

Aidspan describes itself as a US-based non-profit organisation that promotes increased support for and effectiveness of the Global Fund.

Links:

Full text of the president's speech
http://www.whitehouse.gov/news/releases/2003/01/20030128-19.html

White House gets religion on AIDS in Africa
http://www.nytimes.com/2003/02/02/weekinreview/02STOL.html

African nations applaud Bush plan to fight AIDS epidemic
http://www.nytimes.com/2003/01/29/international/africa/29cnd-aids.html

Bush plan for $15 billion to combat AIDS in Africa stuns friends and foes alike
http://www.hivandhepatitis.com/recent/developing/012903k.html

George Bush and the use of language
http://archives.healthdev.net/af-aids/msg00746.html

New York Times leader: A serious response to AIDS
http://www.nytimes.com/2003/02/01/opinion/01SAT2.html

More reports
http://www.kaisernetwork.org/daily_reports/rep_hiv.cfm#15741

Aidspan
http://www.aidspan.org

Global Fund to Fight AIDS, TB and Malaria
http://www.globalfundatm.org/

C O M M E N T

President Bush's decision to spend significantly more money combating HIV in the developing world sets a welcome example to other rich countries that have yet to respond adequately to the global crisis. Until now the UK has had a comparatively good record with the Chancellor of the Exchequer, Gordon Brown, and the Secretary of State for International Development, Clare Short, leading the arguments for greater action backed by greater spending. But their efforts are now dwarfed by the scale of the American response.

It is a shame that President Bush undermines the goodwill and respect his decision to treble overseas spending on the response to AIDS should earn by the decisions on *how* the money will be spent and serious unanswered questions.

Firstly, it is strange to decide that the spending will be limited to 14 nations over the next five years regardless of how the pandemic and our knowledge of it develop.

Secondly, it would have been sensible to channel the resources through the Global Fund to Fight AIDS, TB and Malaria, which is short of money, takes a global view of priorities and is committed to maintaining a slim bureaucracy capable of taking rapid decisions. It is pointless and wasteful for the US to create a parallel bureaucracy competing for the same resources.

The election of Tommy Thompson to chair the Global Fund should indicate a commitment by the richest nation to support the fund and might have suggested that financial support would follow. This is clearly not to be. It appears that America wants to control how it spends its money, and how money given by other nations is spent. This raises serious questions about Mr Bush's motives. Since becoming president he has diverted funding from US and overseas projects that give advice on abortions, and the fear has to be that this devoutly Christian president may use his control of these huge sums to impose his views of morality on others.

While the new money is welcome and responds to the crisis on the scale required, the announcement also deserves to be met with scepticism because of Mr Bush's record in confusing public health and private morality, because of the loaded language he used in his State of the Union address about "innocent people" – suggesting some are guilty and therefore perhaps less deserving? – and because he seems to have acted in a way that prioritises his administration having maximum power over the money rather than making sure the money goes where it is most needed.

The new Global Fund Observer should widen its remit and keep an eye not only on the Global Fund but also act as a watchdog on Mr Bush's billions.

The New York Times points out that by saying that treating HIV can now cost as little as $300 per patient per year, a price only available from manufacturers of generic drugs, Mr Bush appears to endorse the spending of US tax dollars on generic drugs, a move that may upset the big pharmaceutical companies (which have close ties to Mr Bush) but which would see millions more people treated for the same amount of money.

The new funding throws down a challenge to other nations to respond. Had the American money been channelled through the Global Fund that challenge would have been all the more irresistible. The European Union has yet to give to the Global Fund. Europe could show the president the error of his ways by giving a similar sum to the Global Fund. And it must not delay further: in an exploding pandemic money is more effective the sooner it is spent.

The World Health Organisation must continue its work on access to medicines in developing countries

Nathan Ford; Jean-Michel Piedagnel, Médecins Sans Frontières

"The global privatisation of public health is one of the biggest challenges facing the World Health Organisation (WHO), as it is the only body whose absolute objective is to promote and protect health...

"One example is the need to dramatically increase access to affordable antiretrovirals for the estimated 5.7 million people with AIDS who currently need treatment but are left without... For a long time, WHO was absent from the debate surrounding the impact of trade agreements on access to medicines, and every attempt to involve itself in this issue met with fierce opposition from governments, whose first interest is the economic growth of their domestic industries. Thankfully this has changed in the past year and WHO has shown itself to be a powerful and necessary advocate for putting health concerns above trade.

"One of the most pressing issues in the health-trade arena today is that of the right of countries to produce generic medicines for export to other countries. Without an adequate solution, the poorest countries of the world that lack pharmaceutical production capacity of their own will be dependent upon the benevolence of multinational pharmaceutical companies. While others involved in the World Trade Organisation negotiations tried to limit the scope of diseases that might benefit from generic imports, or even prevent any solution from being found, WHO spoke out in clear support for allowing medicine production and export as an exception to patent rights. This work must continue...

"There have been recent signs of WHO reasserting itself as an international standard-setting body, in spite of considerable resistance. The pre-qualification system for the procurement of medicines such as antiretrovirals, which would allow developing countries to find the best price for quality medicines, was established in spite of enormous opposition, and needs to be supported and expanded as a core activity of the organisation's work...

"...In the face of rising infectious diseases such as AIDS, TB and malaria, and the increasing marginalisation of health problems that do not affect the developed world, the importance of an international, independent organisation that is brave, aggressive, and vocal in its defence of global public health has never been more important."

The authors are Médecins Sans Frontières' Access to Medicines Advisor Nathan Ford and UK Executive Director Jean-Michel Piedagnel.

Dr Jong-Wook Lee nominated to be WHO director-general

Dr Jong-Wook Lee was nominated by the World Health Organisation's Executive Board for the post of director-general of the agency. The director-general is WHO's chief technical and administrative officer and sets the policy for the organisation's international health work. The nomination is expected to be confirmed in May.

Dr Lee, aged 57 and from Seoul, Republic of Korea, trained at Seoul National University and the University of Hawaii.

He has worked at WHO for 19 years in technical, managerial and policy positions, notably leading the fight against two of the greatest challenges to health and development: tuberculosis and vaccine preventable diseases of children. After heading the WHO Global Programme for Vaccines and Immunisations and serving as a Senior Policy Advisor, he became, in 2000, Director of the Stop TB programme, a coalition of more than 250 international partners including states, donors, non-governmental organisations, industry and foundations.

Dr Lee speaks English, Korean and Japanese, and reads French and Chinese.

Currently chaired by Professor Kyaw Myint, the 32-member WHO Executive Board heard oral presentations of each candidate's vision of the future priorities and challenges for the organisation and questioned the applicants. At the end of January, it voted on the five short-listed candidates.

His name will be submitted for approval to the 56th World Health Assembly in Geneva in May 2003.

Dr Lee will succeed Dr Gro Harlem Brundtland whose decision not to stand for a second term was announced in August last year. The new director-general will take office and start his five-year term on 21 July 2003.

Source: World Health Organisation

Webcast of the first ever public forum of WHO Director General candidates answering questions about the most critical issues in global health today:
http://www.kaisernetwork.org/healthcast/who/19jan03

Coverage of election in The Lancet:
http://www.thelancet.com/journal/vol361/iss9352/who_director_general_election

Link:
http://www.who.int/en/

AAI Pharma access programme providing treatment for 36,000 people in Africa

Simon Collins, HIV i-Base

The current status of the Access Alliance Initiative (AAI) was outlined to press and community meetings on 14 January in London. The AAI group is a partnership between five United Nations organisations and six major pharmaceutical companies involved in HIV treatment and diagnostics. [1, 2]

Largely as a response to the heightened political awareness of the inequalities of access to care at the International AIDS Conference in Durban in 2000, but partly also in response to the availability of cheaper generic alternatives, each company has reduced prices of drugs by around 85-95%, and in some cases developed donation programmes and generic licensing agreements.

Accessing treatments at these reduced costs requires active involvement at national level of governmental agencies and a decision from each country to actively tackle HIV. Of 80 countries who have so far approached AAI, 40 have developed plans for action and 19 countries have programmes now agreed and in place.

It was stressed that improving health and life expectancy for people living with HIV in Africa involves developing relevant health

infrastructure as well as providing drugs themselves. Individual initiatives developed by many of the pharmaceutical companies in the AAI directly address improving this structure.

On a global scale this initiative has led to access to treatment for perhaps less than 0.5% of HIV positive people in Africa over two years, but it has provided treatment for 36,000 people who would otherwise have gone without. More importantly it has generated a structure upon which increased access to care can be developed.

At the World AIDS Conference in Barcelona in 2002, WHO suggested a goal of three million people on treatment by 2005. This figure is seen as an unrealistically optimistic practical challenge by many agencies aware of the current health care structures that currently exist. It was also seen as appallingly pessimistic given that currently over 40 million people are now infected with HIV.

The Barcelona Conference also contained frequent references to the political will required by Western countries to contribute to the estimated $10 billion-a-year Global Fund to Fight AIDS, TB and Malaria and the difficulties of maintaining a sense of urgency when many people believe the myth that 'AIDS is over' whereas the catastrophe is still gaining momentum on a global scale.

Several other practical issues were raised at the meeting, including:

Whether use of triple combination for the final week of pregnancy could be developed by AAI, given that use of single dose nevirapine put mothers at high risk for developing resistance without reducing transmission risk to levels that would be acceptable in Western countries.

Whether individuals from countries working with AAI are able to purchase and access treatment at these reduced prices.

The level of care accessed remains an important issue. Just over two-thirds of people accessing treatment through this initiative are using combination therapy containing three drugs, but this leaves around one third who will obtain much more limited benefit from using two-drug therapy, which is widely accepted as sub-optimal care in the West.

Although the focus for the AAI programme is Africa, high infection rates have recently been recognised in China, India and Eastern Europe.

Manufacturers of generic drugs currently produce triple combinations at less than $300 for a year's treatment which AAI maintains are close or similar to treatments available under their programme. AAI says that cost is not the only issue. Generic manufacturers have been invited to join the AAI intiative but none have yet done so.

Jeffrey Sturchio, who leads the Merck initiative in the programme recognised that the programme was still just scratching the surface of the problem and that more political will and resources were required. This is "like trying to change a tyre on a car that's going at 100 kilometers an hour - but you still have to try".

References

1. UNAIDS Secretariat, WHO, UNICEF, UN Population Fund, World Bank
2. Abbott Laboratories, Boehringer-Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, F.Hoffman La-Roche, Merck &Co.

Links:

http://www.kaisernetwork.org/daily_reports/rep_index.cfm

http://ww2.aegis.org/news/re/2003/RE030106.html

Pharmacia to launch pilot programme for expanding access to medicines in the poorest countries

In conjunction with a panel discussion in Davos, Swizerland sponsored by the World Economic Forum's Global Health Initiative, Pharmacia Corporation announced the launch of a pilot programme as a model for expanding access to needed medicines for the poorest populations in the developing world. Under the programme, Pharmacia, in partnership with the International Dispensary Association Foundation (IDA), will grant non-exclusive licences for delavirdine (DLV Rescriptor) to generic pharmaceutical companies that agree to manufacture and supply the product to the world's poorest countries.

DLV is an oral, non-nucleoside reverse transcritpase inhibitor (NNRTI), developed by Pharmacia for use in patients with HIV infection. Delavirdine was approved and launched in the United States in 1997 and is among the antiretroviral therapies recommended by the US Department of Health and Human Services for treatment of HIV/AIDS.

Under the not-for-profit pilot programme, Pharmacia will transfer its proprietary manufacturing technology and regulatory dossier for DLV to IDA. IDA, in turn, will be empowered to select any generic companies that meet its quality manufacturing standards. As the world's largest non-profit supplier of generic medicines to developing countries and relief agencies, IDA is uniquely positioned to facilitate manufacturing and supply of generic DLV in eligible countries.

The pilot programme has the potential to benefit HIV/AIDS patients in 78 developing countries including all of the countries in sub-Saharan Africa.

Source: Pharmacia PR

Links:
http://164.109.61.198/newsroom/script_press.asp?id=376

Report from Wall Street Journal

http://www.natap.org/2003/Jan/012403_1.htm

Heineken to offer antiretroviral drug coverage to African workforce

Heineken brewery is at the "leading edge of an effort by multinational [companies] ... to forestall a wipeout of Africa's labour force," by guaranteeing antiretroviral drug coverage to its African workforce of 6,000 and their "immediate dependents," Forbes reports.

Over the last year, Heineken has offered antiretroviral drugs to its employees in Rwanda and Burundi, and is beginning the programme in Nigeria, Ghana, the Democratic Republic of the Congo and the Republic of the Congo. Countries with "rickety hospitals and laboratories," such as Sierra Leone and Chad, or countries where Heineken has a minority stake in breweries, such as Angola and Morocco, will be last, Forbes reports.

Heineken has hired not-for-profit PharmAccess, which trains local doctors to administer the antiretroviral drugs, to run the $2 million-a-year programme. In one brewery that employs 600 workers, Heineken was losing an average of 10 workers or dependents a year to AIDS-related deaths, but last year it lost only one worker, who refused the drug treatment. "If we don't do anything and say, 'Okay, let nature take its toll,' then within seven years 20% of your senior management (in Africa) is gone," Hans van Mameren, head of Heineken's AIDS programme, said. However, the programme "has been a struggle" because only 30% of the workforce in Rwanda has taken an HIV/AIDS test, Forbes reports. Furthermore, Heineken's medical staff "has to make up rules as it goes along" because the eight-page company AIDS manual does not specify exactly what constitutes a dependent; in some of the countries it is legal to have up to four wives, according to Forbes.

Heineken must also deal with the Nigerian government, which charges a 20% import duty on all medications, and airlines that do not want to carry HIV-infected blood from countries without good laboratories for testing. Other problems include ensuring that employees do not resell the drugs and ensuring that employees pay a "token contribution" toward treatment in order to encourage HIV-positive patients to maintain their drug regimens, Forbes reports. "We can't give drugs away for free, or we become an NGO," van Mameren said (Sansoni, Forbes, 2/3).

Link:
http://www.forbes.com/forbes/2003/0203/064.html

Five pharmaceutical companies to halve antiretroviral drug prices for central America

Five pharmaceutical companies - Boehringer Ingleheim, Bristol-Meyers Squibb, GlaxoSmithKline, Roche and Merck – have agreed to reduce the cost of antiretroviral drugs by an average of 55% for six Central American countries, Xinhua News Agency reports. The agreement, which was signed by pharmaceutical company representatives and health ministers from Costa Rica, Guatemala, Honduras, El Salvador, Nicaragua and Panama, will reduce the price of antiretroviral therapy from between $2,500 and $2,800 a year per patient to between $1,035 and $1,453 per year per person, according to Associated Press.

"With these prices we will be able to significantly expand the number of persons receiving antiretroviral treatment for HIV/AIDS in the region," Fernando Garcia, health minister from Panama, said. The agreement, coordinated by the Central American Social Integration Department and thePan American Health Organisation, requires the governments to also establish "clinical management, laboratory monitoring, infirmary and socio-emotional support." According to UN figures, an estimated 180,000 people in central America are HIV-positive and some 16,000 people have AIDS.

Links:

http://www.paho.org/

http://news.xinhuanet.com/english/2003-01/30/content_713181.htm

Patent law overrides would not expand access to drugs for low-income nations, opinion piece says

The United States' insistence in World Trade Organisation talks that patent overrides for low-income nations only apply to drugs to fight specific diseases, such as AIDS, tuberculosis and malaria, is one instance in which "the United States is right, while our usual allies ... are wrong," John Calfee, a resident scholar at the American Enterprise Institute, writes in a Washington Times opinion piece.

Advocates of the plan being considered - which mandates some patent protections be relaxed to allow low-income nations access to drugs - have "fallen for a simplistic argument," Calfee writes. Although proponents of the plan say it is "better to sacrifice a little profit and help the sick poor," Calfee argues that "cheaper drugs tend to get trans-shipped to destinations where prices are higher," and that low-cost drugs "arouse envy" in nations paying full prices.

According to Calfee, patents and prices are "usually not even the same problem"; instead, he states that health care infrastructures must improve. "Until these nations get rudimentary health care markets, rule of law and honest governments, drug prices will remain largely irrelevant," he writes. In lieu of dropping patent law in some countries, the international community should "fac[e] the fact that the anti-patent approach to improving public health has failed and needs to be replaced with patent protection and a willingness to buy the cures that research creates" (Calfee, Washington Times, 1/28).

Source:
http://kaisernetwork.org

http://www.kaisernetwork.org/daily_reports/print_report.cfm?DR_ID=15746&dr_cat=1

ANTIRETROVIRALS

Efficacy and safety of a quadruple combination Combivir + abacavir + efavirenz regimen in antiretroviral treatment-naive HIV-1-infected adults: La Francilienne

Randomised, controlled clinical trials have demonstrated the therapeutic benefits of triple antiretroviral therapies including a protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a nucleoside reverse transcriptase inhibitor (NRTI). Such treatments offer effective, durable control of viral replication, immune restoration, and in some cases delay in the progression to AIDS or death. However, long-term toxicities associated with PI-containing regimens, and potential difficulties with adherence to such therapies, can lead to the development of viral resistance, treatment failure, and limited options for successful subsequent therapy.

The current study, CNAF3008, represents an effort to find PI-sparing, compact and potent regimens to treat ART-naive adults, and to evaluate long-term safety, tolerance, and efficacy. The study tests a regimen combining three nucleosides, Combivir (3TC+ZDV) and abacavir (ABC, Ziagen) with an NNRTI, efavirenz (EFV, Sustiva). The study is a pilot using small patient numbers because of limited prior experience combining abacavir with efavirenz. The researchers performed clinical and biological assessments at baseline and at weeks 2, 4, 8, 16, 24, 32, 40, and 48.

Five women and 26 men, median age 35, enrolled in the study. Median viral load at entry was 4.69 log10 copies/mL (3.1-6.2). Median baseline CD4 cell count was 322 cells/mm (range, 98-858). Eighty-seven percent of patients experienced at least one study-related adverse event (AE); nausea and vomiting were the most common, followed by dizziness/vertigo, malaise and fatigue, skin rashes, and sleep disorders. Subjects reported six serious AEs: five cases of depression, and one of abdominal pain. The authors did not observe definite hypersensitivity reaction to abacavir.

Median cholesterol levels increased significantly, as did fasted glucose. No significant differences were detected for fasting triglyceride measurements. The study did not report any clinical signs or symptoms of lipodystrophy. Patient self-questionnaires reflected a very good adherence level, with 83% and 90% of participants at weeks 24 and 48, respectively, reporting they had not missed a dose or had missed doses less than once a week in the four preceding weeks.

The study demonstrated that a PI-sparing quadruple regimen can lead to a profound and sustained decline in plasma HIV-1 RNA levels. Participants experienced mild to moderate, expected side effects. The combination of drugs led to profound, rapid decline in VL, with a median reduction of 2.7 log10/copies mL as early as week four.

"All patients who remained on the quadruple regimen of ABC/COM/EFV reached VL<50 copies/mL through 48 weeks, irrespective of baseline VL," the authors wrote. "The results of our pilot study allow the start of larger comparative studies of triple versus quadruple therapy.

Ref: Pierre de Truchis; Gilles Force; Yves Welker et al. Efficacy and Safety of a Quadruple Combination Combivir + Abacavir + Efavirenz Regimen in Antiretroviral Treatment-Naïve HIV-1-Infected Adults: La Francilienne. *Journal of Acquired Immune Deficiency Syndromes*,10.01.02; Vol. 31: P. 178-182;

Source: CDC
http://www.thebody.com/cdc/news_updates_archive/2003/jan16_03/la_franciliene.html

http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12394796&dopt=Abstract

Subtle decreases in stavudine (d4t, Zerit) phenotypic susceptibility predict poor virologic response to stavudine monotherapy in zidovudine (AZT, Retrovir)-experienced patients

Researchers at Stanford University School of Medicine in California wanted to identify the level of phenotypic susceptibility for stavudine (d4T, Zerit) that is associated with a diminished virologic response to d4T therapy, so they performed phenotyping on archived baseline HIV isolates from 26 subjects who received d4T monotherapy in AIDS Clinical Trial Group 302 who had receieved >3 years of prior zidovudine (AZT, Retrovir) monotherapy.

Seven of 26 subjects achieved a virologic response of >0.3-log10 copies/mL reduction in plasma HIV RNA after eight weeks of d4T. Responders had lower fold changes in susceptibility to d4T (1.0 vs. 1.6, p = .003), lower baseline viral loads (4.26 vs. 4.74 log10 copies/mL, p = .004), and fewer thymidine analogue mutations (TAMS) (1 vs. 2, p = .059). Lower baseline d4T fold change in susceptibility predicted greater reductions in HIV RNA from baseline to week eight after adjusting for baseline HIV RNA, ZDV fold change in susceptibility, and number of TAMS.

Using the same phenotypic assay, drug susceptibility among 240 antiretroviral-naive patients found all HIV isolates to have d4T susceptibility <or=1.4-fold change. Using <or=1.4 as the d4T cutoff, the positive predictive value for a virologic response in this study was 44%, and the negative predictive value was 100%. d4T susceptibility greater than 1.4-fold change was associated with failure to achieve significant viral load reduction after eight weeks of d4T monotherapy.

Ref: Shulman NS, Hughes MD, Winters MA et al. Subtle decreases in stavudine phenotypic susceptibility predict poor virologic response to stavudine monotherapy in zidovudine-experienced patients. J Acquir Immune Defic Syndr 2002 Oct 1;31(2):121-7
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12394789&dopt=Abstract

RESISTANCE

Medical care providers have very limited knowledge of resistance-associated drug mutations

Graham McKerrow HIV i-Base

A study of New York medical care providers attending an AIDS conference found they had “markedly limited” knowledge of resistance-associated drug mutations and that most incorrectly interpret test results.

The majority of providers questioned used interpretations provided by laboratories and few said they used guidance from recognised experts in resistance testing.

Researchers from the Elmhurst Hospital Centre and the Mount Sinai School of Medicine, New York, distributed an anonymous questionnaire at a meeting for HIV care providers organised by the International AIDS Society-USA in 2001.

The 100 providers who used genotypic testing and returned the questionnaires include 23 nurse practitioners and physician’s assistants and 77 physicians. They were given a list of six drug groups and a list of 16 resistance-associated point mutations and were asked to write next to each drug group the point mutations associated with resistance to that drug.

The results show that 17% of respondents correctly identified at least one resistance mutation for each of six drug groups, whereas 3%, 4%, 10%, 16% and 14% correctly identified resistance mutations for 5, 4, 3, 2 and 1 drug group respectively.

Thirty-six per cent of providers were unable to correctly identify resistance mutations for any of the six drug groups. The average number of drug groups for which providers correctly identified resistance mutations was two.

The researchers report that there was no difference in knowledge among providers on the basis of degree or specialty. Provider patient load was significantly associated with improved knowledge of resistance mutations; those caring for >50 patients were more apt to correctly identify resistance mutations for >or=4 drug groups than were those caring for <or=50 patients (37% vs. 6%; *P* = .001). Knowledge also was better among self-described experts, with 8 (53%) of 15 having knowledge of resistance mutations for >or=4 drug groups (*P* = .01).”

In a substudy analysis, the rersearchers found that of the 38 physicians caring for 100 patients or more 12 (32%) could identify resitance mutations for four or more drug groups., and eight (21%) were unable to correctly identify resistance mutations for any of the drug groups.

The researchers write of the substudy group: “Because of their greater patient load, these physicians were considered more likely to be HIV-dedicated clinicians. Despite their greater patient load, they exhibited a similar limited knowledge of resistance mutations, which suggests that our overall results may, in fact, be representative of HIV care providers in general.”

The authors introduce their report by writing: “Resistance to antiretroviral agents is an important challenge facing providers of care to patients with human immunodeficiency virus. Prospective clinical trials have demonstrated improved short-term virologic outcomes when the choice of antiretroviral drugs was aided by genotypic testing, with further improvements seen when interpretations were guided by experts. Major guidelines recommend the use of genotypic testing to guide treatment changes and emphasize the importance of expert interpretation.

“Evaluating genotypic test results is complex, and laboratory-provided interpretations do not follow a universal standard. For proper interpretation, clinicians must have a basic knowledge of relevant resistance-associated genotypic mutations and must recognize the extent to which they affect susceptibility to specific drugs.”

Their Discussion concludes: “These data highlight problems with the current approach to the interpretation of genotypic testing by clinicians. A standardized algorithm of genotype interpretation that is continually updated and used by all laboratories that perform genotypic testing would be valuable. However, providing more education to HIV specialists about genotype interpretation and improving their access to well-defined recognized experts in the field of HIV resistance are most important.”

Ref: Salama C, Policar M, Cervera C. Knowledge of genotypic resistance mutations among providers of care to patients with human immunodeficiency virus. Clin Infect Dis 2003 Jan 1;36(1):101-4
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12491209&dopt=Abstract

http://www.natap.org/2003/Jan/012403_3.htm

C O M M E N T

This highlights the importance of the expert interpretations that are provided with all resistance tests performed in the UK and the additional consultation expertise provided by the laboratories that run these assays should be utilised.

It is worth re-emphasing that tests, whether genotypically or phenotypically based, only provide an indication of drug sensitivlty to the antiviral agents used in the current or most recent combination. A full indication of drug resistance needs to take into account an individual’s lifetime treatment history and drug exposure.

Inhibitory quotient useful as indicator of effective protease inhibitor therapy

By Brian Boyle, MD, HIVandHepatits.com

Clinicians and patients are well aware that the development of resistance is a significant problem in achieving long-term success with highly active antiretroviral therapy (HAART). It must be recognised, however, that resistance is not an all or none phenomena, but instead comes in gradations.

These gradations are defined by the increase in the inhibitory concentration of a particular drug to a level higher than that of wild-type viruses. Thus, in some cases viral resistance can be overcome by simply increasing drug exposure, something that is routinely done when ritonavir is used in protease inhibitor (PI)-experienced patients to boost other protease inhibitor concentrations to levels sufficient to suppress the mutated virus.

In several recent trials, the use of the Ctrough/IC50 ratio (Inhibitory quotient or “IQ”) has been found to be a useful marker of antiretroviral efficacy. In a study published in AIDS, the clinical usefulness of the IQ as a predictor of virological response was evaluated in two different dual PI regimens.

The study enrolled 52 patients who were on HAART consisting of two nucleoside analogues with either ritonavir/indinavir or nelfinavir/saquinavir and, at baseline, had a median CD4 cell count and viral load of 232 cells/mm3 and 4.2 log10 copies/mL. The enrolled patients had extensive previous antiretroviral (median time 56 months) and PI (median time, 27 months) exposure.

At baseline, the fold increase in the protease inhibitor IC50 values correlated with the patient’s previous PI exposure and was a median of 25.4-fold in indinavir, 108.5-fold in ritonavir, 14.5-fold in nelfinavir, and 2.5-fold in saquinavir.

After at least 15 days on the PI therapy (mean 21 days), pharmacokinetic values used to calculate the PI IQ were obtained. The investigators found a linear relationship between increasing IQ values and a higher HIV-RNA level decrease.

For patients treated with indinavir, the mean HIV decrease was -0.83 and -1.2 log10 copies/ml with an IQ below or above 1, respectively (P = 0.09). Similar results were obtained for ritonavir-treated patients, with a mean decrease of -1.2 log10 copies/ml with an IQ greater than 1. For nelfinavir, the mean HIV-RNA level decrease was -.51 log10 copies/ml with an IQ less than 1 and -1.68 log10 copies/ml with an IQ greater than 1 (P = 0.04). In saquinavir-treated patients, the rate of decrease was -0.92 and -1.1 log10 copies/ml (P = 0.03).

The authors conclude: “This study suggests that it is possible to improve the rate of response by reaching higher drug levels than the IC50. In other words, it demonstrated that the use of available phenotypic testing and the knowledge of the Ctrough reached in every patient may be a useful tool in salvage regimens.

“However, the difficulties with this lie in the uncertainty as to what levels of drugs, relative to in-vitro inhibitory values, are required to achieve optimal efficacy, the lack of standardisation of pharmacokinetic data in PI, and the variability of drug levels among patients. Therefore, we can not establish an ideal IQ to be reached in a dual PI combination.”

Ref: J Casado et al. Individualizing salvage regimens: the inhibitory quotient (Ctrough/IC50) as predictor of virological response. AIDS 2003;17:262-264.

METABOLIC TOXICITIES AND SIDE EFFECTS

30-year study links vitamin A to risk of fracture in humans

Graham McKerrow, HIV i-Base

Swedish researchers have concluded from a 30-year study of 2,322 men that current levels of vitamin A supplementation and food fortification in many western countries may need to be reassessed.

The findings of their study are consistent with the results of animal studies, but no biologic marker of vitamin A status had been used to assess the risk of fractures in humans.

From 1970 to 1973 the researchers from University Hospital, Uppsala, enrolled the men, born between 1920 and 1924 in a population-based, longitudinal, cohort study. The base-line evaluation included a medical and lifestyle questionnaire and interview, tests of serum samples and anthropometric measurements. At 60 years of age, 1,860 men (80% of the total cohort) took part in a second evaluation, and at 70 years, 1,221 men (53%) took part in a third evaluation. Fractures were documented in 266 men in the 30 years of follow-up.

Karl Michaelsson and colleagues report that the risk of fracture was highest among men with the highest levels of serum retinol. Multivariate analysis of the risk of fracture in the highest quintile for serum retinol (>75.62 mg per decilitre [2.64 mmol per litre]) as compared with the middle quintile (62.16 to 67.60 mg per decilitre [2.17 to 2.36 mmol per litre]) showed that the rate ratio was 1.64 (95 percent confidence interval, 1.12 to 2.41) for any fracture and 2.47 (95 percent confidence interval, 1.15 to 5.28) for hip fracture. The risk of fracture was further increased within the highest quintile for serum retinol. Men with retinol levels in the 99th percentile (>103.12 mg per decilitre [3.60 mmol per litre]) had an overall risk of fracture that exceeded the risk among men with lower levels by a factor of seven (P<0.001). The level of serum beta carotene was not associated with the risk of fracture.

The researchers write: “Our findings are consistent with the results of two previous prospective epidemiologic investigations that examined dietary retinol intake and the risk of hip fracture in women. Our study, in which retinol was used as a biologic marker together with the overall risk of fracture, corroborates the detrimental effect of excess retinol on human bone. Serum retinol has been positively associated with both dietary vitamin A intake and use of supplemental vitamin A in most studies but not all. As in the two previous epidemiologic dietary studies, we compared the risk of fracture among subjects who had an estimated dietary vitamin A intake of more than 1.5 mg per day with the risk among those whose intake was less than 0.5 mg per day. All three studies showed that the risk was increased by a factor of approximately two among subjects in the highest category of vitamin A intake.”

Ref: Karl Michaelsson, Hans Lithell, Bengt Vessby et al. Serum retinol Levels and the Risk of Fracture. New England Journal of Medicine, Volume 348:287-294, January 23, 2003, Number 4.
http://content.nejm.org/cgi/content/full/348/4/287

http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12540641&dopt=Abstract

http://www.natap.org/2003/Jan/012303_1.htm

Bone turnover elevated in HIV-positive patients and linked to duration of HAART

Simon Collins, HIV i-Base

Mondy and colleagues from the University of Washington reported results from a longitudinal study looking at prevalence of osteopenia or osteoporosis in HIV-infected persons and assessed bone mineralisation, metabolism, and histomorphometry over time.

128 patients were enrolled in an original cross-sectional study, 93 of whom were then followed for 72 weeks in a longitudinal study. Baseline data included sociodemographic and clinical data, dietary intake history (including vitamin D, calcium, caffeine, alcohol, and average energy intake) together with history of antiretroviral and other medication that may potentially alter bone metabolism. BMI, DEXA and serum and 24-h urine bone markers were taken every six months. Bone biopsy was performed for seven patients who consented to this procedure.

This group was largely a white male group (14% women, 16% non-white). Sixty-eight percent were using a protease-based treatment, 70% had an undetectable viral load and mean duration of treatment was over five years (76 months). Many patients had risks for low BMD such as history of significant weight loss (27%), current or past smokers (35%) low activity level (55%) and calcium intake below RDA (70%).

Almost half (46%) of the patients in the original cross-sectional study had either osteopenia or osteoporosis, confirming findings of previous reports that this is a widespread issue for HIV-positive patients. Osteopenia was more common in people with a history of smoking (44% vs 28%, p=0.06) or previous steroid use for longer than one month (10% vs 2.9%, p=0.08) or previous weight loss (37% vs 19%, p=0.04). Strong associations were found with low current weight, BMI, whole body fat mass, trunk fat mass and peripheral fat mass (all p <0.01). Duration of HIV therapy was the only other factor strongly associated with osteopenia (p=0.05).

The longitudinal follow up showed a small but significant increase in lumbar and hip BMD over 72 weeks (2.6–0.6% and 2.4%–0.4% respectively, both p<0.01). These mean percentage increases remained significant regardless of duration of HAART. Increases in lumbar BMD correlated with CD4 cell increases and baseline viral suppression. The majority of subjects also had high indices of bone metabolism that remained elevated but generally stable for all patients during the 72-week follow-up period, regardless of type of antiretroviral therapy, immune status, or bone mineral density. The authors also emphasised that traditional risk factors are likely to be more important contributory factors than HAART-related factors.

That no correlation was found between BMD and indices of bone turnover was explained by the results of the seven biopsies which showed that multiple mechanisms are likely to underlie the pathogenesis of HIV-related osteopenia.

Although no link to individual drugs or drug classes was found in this study, it was limited by the length of time people had been on treatment at baseline, and the many treatment changes made by patients prior to and during the study.

The authors conclude that higher markers for bone turnover in patients on HAART therapy is a serious concern and that prospective longitudinal studies from patients in early HIV disease and prior to commencing therapy are still required.

Ref: Mondy K, Yarasheski K, Tebas P et al. Longitudinal Evolution of Bone Mineral Density and Bone Markers in HIV–Infected Individuals. Clin Inf Dis 2003:36:482-90 (15 Feb03)

Abstract:
http://www.journals.uchicago.edu/CID/journal/issues/v36n4/20810/brief/20810.abstract.html

C O M M E N T

Pablo Tebas, one of the authors of this study, presented results at the Retrovirus conference from successful use of alendronate, vitamin D and calcium in HIV-patients with osteopenia and osteoporosis (Oral Abstract 134) - again to be covered in full in the next issue of HTB.

He also commented that although monitoring of BMD is not addressed in current guidelines for management of HIV, guidelines for rheumatic disease recommend routine monitoring for any patient group where incidence of osteopenia and osteoperosis rises to levels as high as 40-60% - the incidence currently reported in the HIV-positive population.

Efavirenz effects worse than reported, study says

Researchers conducted a study at San Francisco General Hospital that suggests a greater incidence rate of severe psychiatric illness resulting from HIV treatment with efavirenz (EFV, Sustiva) than had previously been reported. “The serious side effects are suicidal depression including agitation, aggression and hallucinations,” said Talia Puzantian, an associate clinical professor at the University of California-San Francisco, and a clinical pharmacist in psychiatry at San Francisco General.

Puzantian and colleagues authored a study about efavirenz that was presented at the 40th annual meeting of the Infectious Diseases Society of America (ISDA) in October 2002 in Chicago. Previous reports had stated that serious efavirenz side effects had less than a 2% incidence rate. Puzantian and co-authors questioned the rate after seeing a number of HIV patients on the drug admitted to the psychiatry unit, she said. The investigators undertook a retrospective study of severe psychiatric side effects and central nervous system side effects, comparing a database of HIV patients - from March 2000 to February 2002 - who had discontinued efavirenz with a group of patients who had discontinued nelfinavir (NFV, Viracept). “We wanted to see the numbers in a real-world setting,” Puzantian said. “We looked at substance use and psychiatric illness, and the efavirenz and nelfinavir groups were similar, so we controlled for that.”

The study found that for HIV patients who had discontinued efavirenz because of side effects, the main problems were psychiatric and CNS side effects, she said. Data showed that 18.3% of subjects on efavirenz reported vivid dreams; 14.7% complained of insomnia; 10% were lethargic or fatigued; 8.3% had headaches, and 7.3% had dizziness. Of those symptoms among the nelfinavir cohort, the only side effect that was greater than 1.1% was fatigue, reported by 7.8%. Other CNS effects included nightmares, subjects feeling like they were stoned or had a hangover, and feelings of euphoria, dysphoria, confusion and trouble concentrating. The most common neuropsychiatric effect was depression, reported by 12% of efavirenz subjects and 1.1% of nelfinavir subjects.

Nelfinavir patients reported no other neuropsychiatric effects, while the efavirenz group reported others including anxiety (9.2%), suicidal depression (2.8%), hallucinations (1.8%) and agitation (1.8%). “Be aware that these psychiatric side effects can occur and probably occur more than we think,” Puzantian said. “We can’t really guess who it’s going to happen to, so we shouldn’t assume that if someone doesn’t have a substance use or psychiatric illness that it won’t occur.”

Source: CDCDaily Summaries

Ref: Puzantian T, Lee J, Karasic D et al. Psychiatric Effects Associated with Efavirenz: A Retrospective Study. Annual Meeting of the Infectious Diseases Society of America October 24-27, 2002, Chicago. Abstract 481.

Links:

http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/203687.html

http://www.aegis.org/factshts/network/simple/nelf.html

http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12126226&dopt=Abstract

http://www.idsociety.org/

C O M M E N T

The range of side effects associated with efavirenz has been well reported in clinical trials and it is noted that this was a retrospective analysis from case notes. Efavirenz also remains one of the most potent antiretroviral agents available, and data from the ACTG 384 study is likely to continue its high prominence in recommendations for treatment in national treatment guidelines.

However, the higher discontinuation rate and greater severity in a real life setting is often reported in smaller studies but has received less attention. These results highlight the importance of close attention for symptoms of depression, anxiety, mood alteration or persistent sleep disturbance in individual patients using this drug.

Protease inhibitors and cardiovascular outcomes in patients with HIV-1

HOPS is an ongoing prospective observational cohort in which patients have been continuously recruited and followed up since 1992. Nine clinics in eight cities (Atlanta; Chicago; Denver;Oakland; Philadelphia; Stony Brook, NY; Tampa, Fla.; and Washington DC) serve as study sites. HOPS assessed 5,672 HIV-1-infected patients with a mean age of 42.6 for incidence of myocardial infarction. Eighty-two percent of the participants were men; 38% were nonwhite; 63% were homosexual; 12% were injection drug users; 19% were heterosexual; and 12% had other or unspecified risk factors. Of the patients, 3,247 took protease inhibitors after their 1996 introduction; 2,425 did not.

During the observation period, 21 persons had a myocardial infarction. Nineteen of them were among the 3,247 patients taking protease inhibitors. Two were among the 2,425 patients who did not take the drugs. Researchers also documented 15 instances of angina, 11 among the 3,247 who took protease inhibitors, four among the other group. Data showed no single protease inhibitor to be significantly more likely than the others to be associated with the incidence of myocardial infarction.

The study results “suggest that myocardial infarctions and perhaps angina could arise in patients taking protease inhibitors. The overall frequency of myocardial infarctions rose greatly after protease inhibitors were introduced, and the incidence in

HOPS patients rose after protease inhibitors had been used for a few years," according to the report.

The authors noted that most patients who had a myocardial infarction or an angina episode also had other traditional risk factors, such as smoking, hypertension, hyperlipidemia (a high concentration of lipids in the blood), and insulin resistance associated with diabetes mellitus. They suggested that doctors treating HIV-1 patients with protease inhibitors be aware of the possibly increased cardiovascular disease risk and intervene to stop smoking and to diagnose and treat the other risk factors.

Myocardial infarction is still infrequent, usually occurs in people with other risk factors for cardiovascular disease, and should not detract from the appropriate use of these drugs for patients with HIV-1, they wrote.

Source: CDC NCHSTP Daily Summaries

Ref: Scott D. Holmberg; Anne C. Moorman; John M. Williamson et al and the HIV Outpatient Study (HOPS) Investigators. Lancet (11.30.02) Vol. 360: P. 1747-1748

Full text:
http://www.thelancet.com/journal/vol360/iss9347/full/llan.360.9347.original_research.23343.1

HIV protease inhibitors promote atherosclerosis independent of dyslipidemia

The development of HIV protease inhibitor (PI)-related atherosclerosis may be a direct consequence of increased accumulation of cholesteryl ester in macrophages, rather than secondary to dyslipidemia. Researchers at the University of Kentucky Medical School report these findings in the 15 January online edition of the Journal of Clinical Investigation.

Dr Eric J Smart and colleagues found that treatment with ritonavir, indinavir or amprenavir increases the level of cholesteryl ester in THP-1 macrophages and peripheral blood mononuclear cells (PBMCs). However, when CD36 blocking antibodies were added or macrophages from CD36 knockout mice were used, the cells failed to accumulate sterol.

Thus, they write, "the increase in CD36 was responsible for the increase in cellular cholesterol."

The Lexington-based research team confirmed these findings in vivo by adjusting PI dosages to levels that do not cause dyslipidemia in an LDL-receptor-null mouse model or in apoE-null and apoE x CD36 double-null mice.

In the LDLR-null mice and the apoE-null mice, but not in the double-null mice, CD36 protein and cholesteryl ester levels increased in peritoneal macrophages following eight weeks of treatment with PIs.

According to the report, CD36 increased approximately three-fold after treatment amprenavir, five-fold after indinavir, and 13-fold after ritonavir. Furthermore, "the relative increase in the level of CD36...approximated the measured increase in cholesteryl ester accumulation".

Examination of ascending and descending aortas showed that areas covered by atherosclerotic lesions were significantly larger than in vehicle-treated animals. When PI doses were increased to levels that also caused dyslipidemia, atherosclerosis was further increased, the research team notes.

Based on these findings, Dr Smart's group cautions that monitoring plasma lipid markers may fail to identify patients on PI therapy at risk for atherosclerosis: "A more useful test may be to screen PBMCs from patients for an increase in CD36."

Ref: J Clin Invest 2003. Doi:10.1172/JCI200316261.

Source: Reuters Health
http://www.medscape.com/viewarticle/448320?mpid=9105

HAART-associated hyperlipidaemia linked to low risk for cardiovascular disease (CVD)

Simon Collins, HIV i-Base

Results from one of the more potentially optimistic studies first presented at the 4th International Lipodystrophy Workshop last autumn have been published in full in the 24 January 2003 issue of AIDS. In summary the study found that hyperipidaemia in its HIV cohort was largely due to increased VLDL cholesterol and that this may mean HAART-associated hyperipidaemia may be less of a risk factor for CVD than previously feared.

Increased levels of cholesterol and triglycerides are a well-described side effect associated with HAART therapy and the overlap of symptoms with cardiovascular risk factors has been a cause of concern and focus for research. Although case reports of cardiovascular disease (CVD) in young HIV-positive men and women have been reported, analysis of CVD events from large cohort studies have not proved conclusive. One difficulty with these studies has been their relative short duration and that risk factors for CVD in the HIV-negative population accumulate over 20-30 years.

Dr Stefan Mauss and colleagues from the Centre for HIV and Hepatogastroenterology in Dusseldorf looked at the lipoprotein pattern from fasting serum samples from 187 consecutive antiretroviral-treated and untreated HIV-positive patients and compared these to 10 individuals with familial combined hyperlipidaemia (high cardiovascular risk) and 14 with familial hypertriglyceridaemia (low cardiovascular risk).

Total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, apolipoprotein A1 and B were determined in serum. Very low density lipoprotein (VLDL) was prepared by ultracentrifugation and analysed for cholesterol, triglycerides and apolipoprotein B.

Lipoprotein disorders were found in 114/187 HIV-positive patients (61%). Of these, 10% had elevated LDL-cholesterol, 14% elevated LDL- and VLDL-cholesterol and 76% had elevated VLDL-cholesterol. The ratio of VLDL-triglycerides to VLDL-apolipoprotein B in 34 HIV-positive patients with hyperlipidaemia patients was similar to the 14 patients with famlial hypertriglyceridaemia, but differed substantially from 10 patients with familial combined hyperlipidaemia ($P < 0.0001$).

The authors concluded "that the large subgroup of HIV-positive patients taking antiretroviral treatment and with hypercholesterolaemia caused by increased VLDL may have a lower cardiovascular risk than generally expected. A differentiated analysis of the lipoprotein pattern should be included in prospective studies assessing the cardiovascular risk of HIV-positive patients to test this hypothesis. However, the contribution of other important cardiovascular risk factors frequently found in HIV-positive patients taking antiretroviral treatment, such as insulin resistance, must also be considered in prospective studies."

Ref: Mauss S, Stechel J, Willers R et al. Differentiating hyperlipidaemia associated with antiretroviral therapy. AIDS 2003; 17(2):189-194

Study abstract and extracts:
http://www.natap.org/2003/Jan/012103_6.htm

C O M M E N T

Higher risks of cardiovascular disease associated with antiretroviral treatment was one of the most debated issues at the CROI conference.

The first results from the international D:A:D study (Oral presentation, Abstract 130) indicated that this may be as high as 27% increased risk per year of antiretroval use and was supported by at least one longitudinal study looking at intima media thickness of the carotid artery. These, and other, at first sight, contradictory studies will be reported in the next HTB.

It was emphasised that for many people who are already at a low risk, this increased risk still remains very low and is generally outweighed by the benefits of HAART. For people already in a higher risk group, lifestyle changes including diet, smoking cessation and exercise are even more important. Clearly, a patients risk of cardiovascular disease should be taken into account when prescribing antiretroviral treatment.

Patient on human growth hormone develops tumours with growth hormone receptors

Brian Boyle, for HIVandHepatitis.com

Recombinant human growth hormone (rhGH) has been available for several years and has been shown in studies to be effective, at least while being given, in treating HIV-related wasting and the fat accumulation associated with lipodystrophy.

While effective, several factors have held back the widespread use of rhGH, including its high cost, potential side effects and adverse events and the need for injection. A recent report from Harvard Medical School raises some additional concerns regarding the use of rhGH. In this report, which was recently published in Clinical Infectious Diseases, a patient treated with rhGH for HIV-related lipodystrophy developed growth hormone receptor -expressing carcinoid tumours in the distal colon and rectum.

The patient involved in the report was 40 years old and obese, with a CD4+ count of 584 cells/mm3 and an undetectable viral load on highly active antiretroviral therapy (HAART) that included Crixivan (indinavir), Retrovir (zidovudine) and Epivir (lamivudine). He had a history of a hyperplastic rectal polyp that had been removed 14 months prior to his development of the carcinoid tumors.

After developing lipodystrophy, which included increased abdominal fat, a dorsocervical fat pad and other abnormal fat accumulation, his antiretrovirals were changed and he was started on rHGH.

Initially, the rhGH was tolerated well with only minor arthralgias and some edema of the extremities. However, after receiving rhGH therapy for eight months, the patient presented with painless rectal bleeding. Colonoscopy revealed two sessile polyps in the distal sigmoid colon and rectum, both of which were found to be neuroendocrine cell (carcinoid) tumors without atypical histopathologic features.

Immunohistochemical methods showed both to have marked expression of growth hormone receptor. Therapy with rhGH was discontinued, and the patient has experienced no further episodes of rectal bleeding.

The authors conclude, "Although we describe a patient who developed [growth hormone] receptor-expressing carcinoids while he was receiving prolonged rhGH therapy, a causal relationship can only be assumed. Nevertheless, the case report presented here should serve as a cautionary note regarding the use of potentially oncogenic rhGH therapy for HIV-positive persons.

Until longterm studies have adequately assessed the potential risks associated with GH therapy in this patient population, careful surveillance for malignancies, and, possibly, monitoring of serum levels of [insulin-like growth factor-I (IGF-I)], may be warranted for HIV-positive [growth hormone] recipients. IGF-I testing is commercially available and currently is being used to monitor disease activity in those with acromegaly and to provide prognostic information for patients with cancer."

Ref: L Pantanowitz et al. Growth Hormone Receptor (GH) - Expressing Carcinoid Tumors after Recombinant Human GH Therapy for Human Immunodeficiency Virus-Related Lipodystrophy. Clinical Infectious Diseases 2003; 36:370-372.
http://www.hivandhepatitis.com/recent/malignancies/012903a.html

Review of trials shows testosterone increases lean body mass, and is most effective when given intramuscularly

Graham McKerrow, HIV i-Base

A review of randomised, placebo-controlled trials concludes that testosterone therapy increases lean body mass more than placebo in HIV-positive patients with wasting. And the researchers at St Bartholomew's Hospital in London also conclude that the increase is even greater if the therapy is given intramuscularly.

Anthony Kong and colleagues report that eight trials met the inclusion criteria and 417 randomised patients were included. Only six trials used lean body mass, fat-free mass, or body cell mass as outcome measures and meta-analysis of these showed a difference in lean body mass between the testosterone group and the placebo group of 1.22kg for the random effect model and 0.51kg for fixed effect.

The researchers draw attention to the fact that the difference was much greater in three trials that used the intramuscular route: 3.34kg in the post-hoc analysis.

All eight trials included total body weight as an outcome measure, the meta-analysis of which showed a difference of 1.04kg by random effect and 0.63kg for fixed effect models. The incidence of adverse effects was similar in both groups.

The researchers warn that the study is limited by the small numbers and heterogeneity of the population, but nonetheless they write: "Testosterone therapy may be considered in patients with HIV wasting syndrome to reverse muscular loss, but there is a concern about the adverse metabolic effects of long-term testosterone administration and long-term follow-up for these patients is needed."

Ref: Kong A, Edmonds P. Testosterone therapy in HIV wasting syndrome: systematic review and meta-analysis. Lancet Infect Dis 2002 Nov;2(11):692-9
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12409050&dopt=Abstract

IMMUNOLOGY

Antiretroviral treatment increases adult thymic volume

Michael Greer, Drug Week

Researchers in Spain found that HAART increases thymus size in adult HIV patients. "An important thymus role has been suggested in T-cell repopulation after HAART in adult HIV-1 infected patients," according to A. Rubio and colleagues at the University of Seville and Virgen del Rocio University Hospital in Seville.

The researchers evaluated thymic size in 21 adult HIV patients 12 and 24 weeks after HAART was initiated. They found that HAART significantly improved thymic volume in patients after 24 weeks. The report notes that significant elevations in overall

CD4 cell counts and increased production of naive T cells accompanied the increased thymus size. Previous studies had associated increased thymus size and HAART in paediatric patients.

These data show the first evidence of early change in thymic volume of adult HIV-1-infected patients under HAART," Rubio and colleagues concluded. "This increase was related to the rise of both total and naive CD4+ cell counts suggesting a functional role of thymic volume increase."

Ref: Rubio A, Martinez-Moya M, Leal M et al. Changes in thymus volume in adult HIV-infected patients under HAART: correlation with the T-cell repopulation. Clin Exp Immunol 2002 Oct;130(1):121-6
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12296862&dopt=Abstract

Source: CDC NCHSTP Daily Summaries

OPPORTUNISTIC INFECTIONS

Rituximab and chemotherapy is highly effective in patients with CD20-positive non-Hodgkin's lymphoma and HIV

Sean Hosein, CATIE News

In high-income countries, the availability of highly active antiretroviral therapy (HAART) has led to dramatic decreases in deaths from many AIDS-related complications. This is true particularly of infections. Yet decreases in AIDS-related cancers, such as non-Hodgkin's lymphoma (NHL), have not been as dramatic in the few years since HAART has been available.

To enhance the effectiveness of anti-cancer therapy for people with HIV/AIDS (PHAs), researchers have been testing a novel therapy called Rituxan (Mabthera, rituximab). This therapy consists of antibodies that attack tumours. Researchers in Italy are reporting increased survival in PHAs with certain cancers who receive Rituxan as part of their anti-cancer therapy.

Study details

The research team reported results on 38 HIV positive subjects who were recruited between June 1998 and October 2001. The profile of these people was as follows:

- 15% female, 85% male
- average CD4+ count – 120 cells
- Most were diagnosed with either NHL or another cancer called Burkitt's lymphoma.
- About half the subjects had symptoms such as fever, night sweats, swollen lymph nodes and unintentional weight loss.

Researchers gave subjects standard chemotherapy taken intravenously for "four days every four weeks"; this was called a cycle. Rituxan was given intravenously at a dose of 375 mg per square metre of skin surface, one day before each cycle. Subjects were expected to take at least six cycles of chemotherapy. Bone marrow stimulants and various antibiotics/anti-fungal drugs were also prescribed to reduce the risk of infections that can develop during chemotherapy. In addition, all subjects took HAART.

Results

Here's what happened to the 38 subjects:

- 76% – their tumours disappeared
- 5% – their tumours shrunk but did not go away
- 19% – their tumours continued to grow

Two years after receiving this therapy, the researchers calculated that about 70% of their subjects were still alive, with only 10% of those who were initially cured experiencing a relapse. Most deaths were due to complications from NHL. Encouraged by these results, the researchers are considering a larger clinical trial to confirm their findings.

Technical note

Rituxan belongs to a group of drugs called monoclonal antibodies. It works by locking onto tumours that have a protein called CD20, which is found on certain cancer cells. The antibody helps the immune system destroy the tumour. All subjects in this

study had cancer cells that had CD20. Rituxan is licensed for use in North America and the countries of the European Union.

References

1. Spina M, Sparano JA, Jaeger U, et al. Rituximab and chemotherapy is highly effective in patients with CD20-positive non-Hodgkin's lymphoma and HIV infection. AIDS 2003 Jan 3;17(1):137-8.
2. Manches O, Lui G, Chapero L, et al. In vitro mechanisms of action of rituximab on primary non-Hodgkin lymphomas. Blood 2003 Feb 1;101(3):949-54.

Source: CATIE News
http://ww2.aegis.org/news/catie/2003/CATE-N20030101.html

C O M M E N T

The Italian study used a background chemotherapy of infusional cyclophosphamide, doxorubicin and etoposide and was presented as a poster at the Retrovirus conference. A second study from the French ANRS group reported using rituximab with CHOP chemotherapy in HIV patients with high-grade lymphoma (Abstracts 803 and 804 respectively).

Lung cancer in HIV positive HAART-users

Sean Hosein for CATIE News

By reducing levels of HIV in the blood (viral load) and thus strengthening the immune system, highly active antiretroviral therapy (HAART) has greatly reduced deaths from AIDS-related infections. Since the introduction of HAART in high-income countries, some cancers associated with HIV, such as Kaposi's sarcoma (KS) and lymphoma inside the brain, appear to be decreasing. Unfortunately, though, HAART does not cure HIV infection and some degree of immune deficiency remains, despite continued treatment. As a result, the risk of developing some cancers, such as lymphoma outside the brain, remains higher in people with HIV/AIDS (PHAs) than in HIV negative people.

One cancer in PHAs that has been the focus of attention is lung cancer. This cancer can arise from exposure to tobacco smoke. Some studies have found higher-than-normal levels of cigarette usage in HIV positive people. Since HAART has had an impact on some HIV-related complications, researchers are interested in understanding the impact of HAART on lung cancer. To do this, researchers in London, England, reviewed information in their database of 8,400 PHAs.

Results

In analysing data between 1986 and 2001, the researchers found the following:

- 11 HIV positive people (one female, 10 males) were diagnosed with lung cancer, all of whom were tobacco smokers.
- Nine of the 11 developed lung cancer in the time HAART was available (1996-2001). Six of the nine were taking HAART at the time cancer was diagnosed. The other three had sufficiently high CD4+ cell counts and did not require HAART at the time their cancers developed.
- The response of the tumours to anti-cancer therapy (radiation or chemotherapy) was not good, and half of the subjects did not survive beyond five months after their cancer diagnosis.
- Overall, once diagnosed with lung cancer, survival of PHAs in the time of HAART was not different from survival of PHAs with the same cancer when HAART was not available.

Risks of developing lung cancer

The researchers found that in the time before HAART, the risk of developing lung cancer was about the same in HIV negative and HIV positive people. However, in the years since HAART has become available, the risk of developing lung cancer in HIV positive people has become about eight times greater than that in HIV negative people.

In examining the data in this study and in five other studies, the researchers found that the following factors, which could have had an impact on survival, were similar before and after HAART became available:

- age at the time lung cancer was diagnosed
- number of cigarettes smoked
- level of CD4+ cells at the time lung cancer was diagnosed

The researchers aren't sure why cigarette smokers who use HAART appear to be at increased risk of developing lung cancer as compared to HIV negative smokers. Their speculation is as follows:

HAART helps to partially repair the immune system of PHAs. This partial improvement is enough to protect them from many AIDS-related infections, and therefore prolongs their survival. However, over time, because the immune system has only been partially restored, it cannot always detect the presence of abnormal growths. As PHAs live longer with weakened immunity, abnormal growths can develop into tumours.

Not mentioned by the researchers is the need for smoking cessation programmes for PHAs who smoke tobacco.

References:
1. Gérard L, Galicier L, Maillard A, et al. Systemic non-Hodgkin lymphoma in HIV-infected patients with effective suppression of HIV replication: persistent occurrence but improved survival. J Acquir Immune Defic Syndr 2002 Aug 15;30(5):478-84.
2. Gérard L, Galicier L, Boulanger E, et al. Improved survival in HIV-related Hodgkin's lymphoma since the introduction of highly active antiretroviral therapy. AIDS 2003 Jan 3;17(1):81-7.
3. Bower M, Powles T, Nelson M, et al. HIV-related lung cancer in the era of highly active antiretroviral therapy. AIDS 2003 Feb 14;17(3):371-5.

Source: CATIE News
http://ww2.aegis.org/news/catie/2003/CATE-N20030201.html

Functional MRI can find brain abnormalities in asymptomatic patients

Michael Greer, AIDS Weekly

US researchers found that functional magnetic resonance imaging (fMRI) can offer early warning of neurologic morbidity in HIV patients. "A previous fMRI study demonstrated increased brain activation during working memory tasks in patients with HIV with mild dementia," wrote Thomas Ernst and colleagues at Brookhaven National Laboratory in Upton, NY, the Massachusetts Institute of Technology- Cambridge and the University of California-Los Angeles Medical Center in Torrance.

Ernst and colleagues discovered that fMRI screening could detect neurologic abnormalities even in patients who have no overt symptoms of dementia. The researchers evaluated the utility of blood oxygenation level-dependent fMRI for finding abnormal brain activity. A group of 10 HIV patients with low CD4 cell counts underwent neuropsychological tests under fMRI. The investigators compared their results with those of age-, sex-, education-, and handedness-matched seronegative controls, according to the study.

Although the HIV patients did not suffer from impaired test performance, fMRI showed significant increases in their lateral prefrontal cortex activation and activated brain volume, data revealed. The asymptomatic patients showed heightened activated brain volume in the lateral prefrontal cortex during all of the assigned tasks, regardless of the difficulty. The investigators found that fMRI measurements of brain activity and activated volume were similar in other regions of the brain between patients and controls.

"Increased brain activation in subjects who are positive for HIV precedes clinical signs or deficits on cognitive tests," Ernst and colleagues concluded. " fMRI appears to be more sensitive than clinical and neuropsychological evaluations for detecting early HIV-associated brain injury."

Ref: Ernst T, Chang L, Jovicich J et al. Abnormal Brain Activation on Functional MRI in Cognitively Asymptomatic HIV Patients" in Neurology (2002;59(9):1343-1349).
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12427881&dopt=Abstract

Source: CDC NCHSTP Daily Summaries
http://www.aegis.com/todaysnews/du.asp#3810

HEPATITIS AND COINFECTION

Hepatitis C virus viraemia in HIV-infected individuals with negative HCV antibody tests

Sanjay Bhagani, HIV I-Base

This prospective study looked at the presence of hepatitis C virus viraemia (HCV RNA) in HIV-infected, HCV-antibody negative patients using an 'in-house' whole blood RT-PCR test for HCV RNA. A group of HIV-negative diabetic patients were used as controls. Samples from viraemic patients were then retested using commercially available plasma and serum HCV RNA tests.

Of the 100 HIV-positive, HCV-antibody negative patients, 20 (20%) had HCV RNA detected by the whole blood assay. None

of the 100 HIV-negative, HCV-antibody negative controls had evidence of HCV viraemia (p <0.001). Of the 20, whole blood HCV viraemic patients, 16 were confirmed positive by RT-PCR on a previously obtained serum specimen. Eleven of the 20 patients had further confirmation of the viraemia by amplification and detection using primers from the NS5A region of the genome. Thus 19% of the HCV-antibody negative patients tested HCV RNA positive on two separate sample dates. Using a commercial RT-PCR (Roche Amplicor), six of the 20 patients had RNA detected in plasma using a standard method, and a further three were additionally positive using higher volumes of whole blood in the Roche assay. Therefore only 9% of the HCV-antibody negative population were HCV viraemic by commercially available RT-PCR.

Only one of these patients had a measurable HCV RNA concentration in the quantitative Roche Monitor 2.0 assay, indicating that these patients had low concentrations of HCV RNA present in plasma. By testing for HCV RNA in the earliest plasma or serum specimen available, the mean duration of HCV viraemia was found to be 26.8 months. HCV antibody was negative when repeated on the most recent plasma specimen in these 20 patients thus excluding recent infection with delayed seroconversion.

When demographic risk factors for acquisition of HCV and HIV were compared, HCV-antibody positive, HCV RNA positive patients were more likely to have a history of parenteral exposure than the 20 HCV viraemic seronegative patients (p <0.001).

The parenterally exposed group had a significantly higher mean ALT (87 m/l vs. 38 m/l, p = 0.013) and non-significantly higher initial CD4 counts (211 cells/mm^3 vs. 211 cells/mm^3, p=0.125) than those who acquired HIV sexually.

The authors conclude that whole blood testing for HCV RNA demonstrates a significantly higher rate of HCV infection among patients with HIV infection who are HCV antibody negative. Furthermore, their whole blood in-house RT-PCR assay performed better than a standard commercial assay or a modification of the commercial assay. Although progression of liver disease was not evaluated in their study, they suggest that if the liver biopsy demonstrates significant fibrosis, then HCV therapy should be instituted, and abstinence from alcohol should be encouraged in these patients.

Ref: George SL, Gebhardt J, Klinzman D et al. Hepatitis C virus viremia in HIV-infected individuals with negative HCV antibody tests. J Acquir Immune Defic Syndr 2002 Oct 1;31(2):154-62
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12394793&dopt=Abstract

C O M M E N T

This study demonstrates the significance of HCV RT-PCR in the diagnosis of HCV in immunosuppressed patients who are HCV antibody negative. Other studies have demonstrated that up to 5% of HIV positive patients with HCV infection may not have detectable circulating HCV antibodies (measured by the commercially available ELISA tests). Current practice in most HIV units is where there is a high index of suspicion of HCV co-infection (unexplained elevated hepatic transaminases, extrahepatic manifestations of HCV), and in the absence of HCV-antibodies, an HCV RT-PCR test should be performed on serum or plasma.

In this study, the in-house whole blood RT-PCR picked up 50% more HCV infections than commercially available HCV PCR tests. The increased sensitivity of the whole blood assay, as compared to plasma or serum assays, can probably be explained by reservoirs of HCV in peripheral blood lymphocytes. However, all these patients have very low circulating HCV levels and the clinical significance (either in terms of liver disease progression, or HCV transmission) of this infection has yet to be demonstrated. Of course, lifestyle changes to minimise HCV related liver damage can be made earlier as a result of a more sensitive test.

It is likely that once HCV viral loads increase (and they do significantly in HIV co-infection over time), commercially available RT-PCRs will detect viraemia. Many of these patients, because of the immune defect, may not mount a detectable antibody response.

Although, whole blood HCV RT-PCR tests may be more sensitive in detecting viraemia in HCV antibody negative patients, their use in clinical practice is yet to be determined. For now, commercially available HCV PCR tests remain important diagnostic tools in immune suppressed HCV antibody negative patients.

Roche's Copegus (ribaviran) available in UK for use in the treatment of Hepatitis C

Roche has received approval from the Medicines Control Agency (MCA) for its proprietary ribavirin, Copegus. Copegus is now available for the treatment of chronic hepatitis C in combination with the recently launched Pegasys (40 KD peginterferon alfa-2a) or Roferon A (interferon alfa-2a).

Copegus is indicated in combination with Pegasys or Roferon A for the treatment of adult patients with chronic hepatitis C who have not previously been treated, including patients with fibrosis or compensated cirrhosis. It is also indicated for the treatment of adult patients who have responded to interferon alpha monotherapy but have since relapsed.

Copegus is manufactured by Roche as a light pink, oval shaped, film-coated tablet containing 200 mg of ribavirin.

Pegasys is a new generation hepatitis C therapy. In combination with Copegus, Pegasys is the only pegylated interferon that

offers all patient groups (genotype 1 and non-1), even with difficult-to-treat advanced liver disease. Compared to standard interferon it offers more patients, with even difficult-to-treat and advanced liver disease, a better chance of a cure when compared with non-pegylated interferon. It is given once-weekly by injection and compared to standard combination therapy, Pegasys is associated with a significant reduction in the incidence of certain side-effects such as flu-like symptoms, depression and hair loss.

Source: Roche Laboratories PR
http://www.roche.com

PEG-Intron plus ribavirin in non-responders and relapsers

The pegylated interferons have proven superior to standard interferons as monotherapy for chronic hepatitis C and, more recently, in combination with ribavirin (RBV) in treatment-naïve patients.

The goal of the present study is to compare the efficacy of two dose regimens of PEG-Intron plus ribavirin in patients with prior non-response to interferon (IFN) monotherapy or combination therapy, or with relapse after combination therapy.

Patients in the three categories are randomised in this ongoing trial to receive (1) PEG-Intron 1.0 mcg/kg plus RBV 1000-1200 mg/d (Group 1), or (2) PEG-Intron 1.5 mcg/kg plus ribavirin 800 mg/d (Group 2). Prior therapy must have been stopped at least three months prior to entry. Treatment is planned for 48 weeks, with cessation of therapy if PCR for HCV RNA (Roche Amplicor) remains positive at 24 weeks.

Of 330 patients enrolled to date, 131 have completed 48 weeks of therapy with 24 weeks post-treatment follow-up. Of these, the results of follow-up week 24 treatment PCR by intent-to-treat analysis are shown in the Table below.

Overall SR is 21% across all three patient categories. Patients with normal ALT respond as well as those with elevated ALT at onset of therapy. Among the 330 patients in the entire study who have reached 24 wk of therapy, PCR at 24 wk is negative in 19% of group 1 and 32% in group 2.

Conclusions:

1. Early results indicate that prior treatment failures, even prior non-responders to combination therapy with HCV genotype 1, may respond to PEG-Intron plus RBV. However, sustained response (SR) rates in the genotype 1 non-responders are low thus far, ie 10-12%.
2. Combination therapy relapsers and interferon monotherapy non-responders have higher rates of SR than combination therapy non-responders.
3. No definitive conclusions can be reached until a larger number of patients have been studied and data on SR become available for the entire cohort.

Quantitative PCR <1000 copies/ml at follow-up week 24:

	Gp 1 (n=70)	Gp 2 (n=61)	Total (n=131)
Comb NR genotype 1	5/48 (10%)	4/33 (12%)	9/81 (11%)
Comb NR genotype non-1	1/5 (20%)	0/5 (0%)	1/10 (10%)
Comb relapsers	3/7 (43%)	9/15 (60%)	12/22 (55%)
Interferon NR	4/10 (40%)	2/8 (25%)	6/18 (33%)

Ref: I Jacobson et al. Pegylated interferon alfa-2B plus ribavirin in patients with chronic hepatitis C: a trial in prior nonresponders to interferon monotherapy or combination therapy and in combination therapy relapsers. Abstract 782 (poster). 53rd AASLD. November 1-5, 2002. Boston, MA. Hepatology 2002: Vol 36 No 4, Pt 2 of 2.
http://www.hivandhepatitis.com/hep_c/news/012703b.html

Source: HIVandHepatitis.com

Dangers of HIV/hepatitis B coinfection

Researchers at Johns Hopkins found that men infected with a combination of hepatitis B and HIV are 17 times more likely to die than those with hepatitis B alone. “These results underscore the importance of prevention, treatment and comprehensive management of hepatitis B in people infected with HIV,” said Chloe Thio, lead author of the study and assistant professor of medicine in the division of infectious diseases at Johns Hopkins.

The low rate of liver disease-related deaths in men with hepatitis B alone is consistent with the 20-30 years it typically takes for complications from hepatitis B to develop, Thio explained. However, since HIV and hepatitis B are transmitted the same way, coinfection is common. Up to 10% of the HIV-infected also have hepatitis B. “Our results suggest that HIV increases the severity of hepatitis B infections, and that physicians may see an increase of hepatitis B-related liver disease in the one million people living with HIV in the United States,” said Thio.

Thio and colleagues analysed clinical data and blood and tissue samples from 5,293 men in the Multicenter AIDS Cohort Study from 1994 to 2000. The researchers compared death rates from liver disease for four patient groups: HIV-infected men, hepatitis-B infected men, men with both viruses, and men with no viruses.

They found that 6% of the men (326) had hepatitis B. Of those, 213 (65%) also had HIV. Of the 4,987 men without hepatitis B, 2,346 (47%) had HIV. Liver disease-related death was highest in men with advanced HIV (measured by CD4 cell count) and was twice as high after 1996, when highly effective HIV therapies were introduced.

“Determining possible adverse effects of long-term use of HIV therapies and assessing the possible interaction with hepatitis infections are central questions that our ongoing studies will address,” said Alvaro Mu, professor of epidemiology at the Johns Hopkins Bloomberg School of Public Health.

Ref: Thio CL, Seaberg EC, Skolasky R Jr et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet 2002 Dec 14;360(9349):1921-6
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12493258&dopt=Abstract

Source: CDC News Updates/TheBody.com
http://www.thebody.com/cdc/news_updates_archive/2003/jan10_03/hiv_hepatitis_b.html

OTHER NEWS

SILCAAT IL-2 study saved as investigators take over responsibility and Chiron agrees to continue funding

Graham McKerrow, HIV I-Base

The Chiron Corporation has apparently reversed its decision to stop funding the SILCAAT phase III study of recombinant interleukin-2 (IL-2), and has agreed to hand over responsibility for the trial to the investigators.

The agreement comes three months after an announcement of “a business decision” by the company that it would halt the study because it would take longer and be more expensive than expected.

SILCAAT (Study of IL-2 in people with low CD4+ T cell counts on Active Anti-HIV Therapy) is a randomised, controlled, open label trial of subcutaneous IL-2 that has been following nearly 2,000 people with advanced HIV infection at 137 clinical sites in 11 countries. The trial study is designed to compare outcomes of HIV-positive persons with CD4 cell counts between 50-299/mm3 randomised to receive IL-2 in addition to antiretroviral therapy with a control group of individuals treated with antiretroviral therapy alone.

Chiron completed two scheduled interim analyses of data from the trial, including data from 1,000 patients followed for a year. Participation is expected to last four to six years. The trial continued while Chiron negotiated with the Scientific Committee for SILCAAT.

Chiron said they had expected the study to cost $75 million, but that had now been revised up to $160 million. The announcement that Chiron would halt the trial provoked much criticism of the company.

Announcing the change of heart, Chiron president Craig Wheeler, said: “We did not anticipate the amount of support this trial had in the HIV scientific community.”

Chiron has not said how much funding it will make available to the study but a report in the San Francisco Chronicle said it would give $5 million annually for three to four years, rather than the original promise of $20 million a year for four to five years. A researcher was quoted in the Chronicle saying he feared the study could “fall apart” if colleagues dropped out because they could not cover their costs.

Interleukins signal the immune system to act when it is under attack. Interleukin-2 in particular causes more CD4+ T cells to be produced. During HIV infection, natural IL-2 production gradually declines. Treatment with supplemental IL-2 therapy is being studied as a way to increase CD4+ T cell counts and possibly improve immune function.

Links:

Pharmaceutical company Chiron reverses course, agrees to continue funding study on anti-AIDS treatment interleukin-2
http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=1&DR_ID=15536

Chiron Corporation and SILCAAT principal investigators agree on transfer of trial
http://www.chiron.com/investor/news/index.htm

San Francisco Chronicle: Chiron reversal on AIDS study
http://ww2.aegis.org/news/sc/2003/SC030103.html

Drug industry contributions influence clinical research, JAMA study says

Financial ties between academic researchers and universities and pharmaceutical companies are "pervasive and may impact the research process," according to a study in the Journal of the American Medical Association (JAMA), USA Today reports. The study, titled "Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systemic Review," analysed data from 37 peer-reviewed studies published between 1980 and 2000 to determine the "extent, impact and management of financial conflicts."

The study found that 25% of biomedical researchers at universities had commercial ties "serious enough to raise questions of financial conflict" and in many cases, "enough to skew their research," the Los Angeles Times reports.

The study also found that universities, which are "expected to police the integrity and ethics" of faculty researchers, "have their own commercial research interests" and financial conflicts of interest, the Times reports.

About two-thirds of the universities studied had equity in companies whose research they were supposed to monitor; 27 universities had equity in 10 or more companies.

As result of the conflicts of interest, industry-sponsored research is 3.6 times more likely to have results favourable to the company that funded the research, according to the study (Hotz, Los Angeles Times, 1/22).

The study found that the protocols for industry-sponsored research often "favour the sponsor's drug"; in addition, many researchers will not publish studies with "unfavourable results," and medical journals often do not publish studies with "boring, negative results" for new treatments (USA Today, 1/22).

Future Impact

Industry funds have become the "lifeblood" of biomedical research - they accounted for 62% of US expenditures on prescription drug research by 2000 - but fewer than half of 47 of the "most influential" medical journals have disclosure policies to "alert the public to the possibility of bias," the Times reports.

In addition, although most universities and medical centres have disclosure policies, they often do not adhere to them in practice (Los Angeles Times, 1/22).

There is a lot of idealism about how science is isolated and objective," Virginia Ashby Sharpe, a bioethicist at the Center for Science in the Public Interest, said, adding, "Unfortunately, that's not the case. Money can absolutely influence scientists" (USA Today, 1/22).

According to the study, because a "convergence of pressures ... will likely lead to increased reliance on industry financing" for biomedical research in the future, "close scrutiny will be required to understand and monitor the unintended consequences of academic-industry collaboration" (Bekelman et al., JAMA, 1/22).

Ref: JE Bekelman et al. Scope and Impact of Financial Conflicts of Interest in Biomedical Research. A Systematic Review. *Journal of the American Medical Association (JAMA)* 2003;289:454-465.

Source: JAMA

JAMA abstract:
http://jama.ama-assn.org/issues/v289n4/abs/jrv20091.html

Accuracy of pharmaceutical advertisements in medical journals

An article by Pilar Villanueva and colleagues in The Lancet reviews the accuracy of claims made in advertisements for antihypertensive and lipid-lowering drugs in Spanish medical journals. Advertisements were largely in prestigious journals and

were referenced by strong studies, but nearly half of the promotional statements were not supported by the associated reference.

The authors concluded that 'doctors should be cautious in assessment of advertisements that claim a drug has greater efficacy, safety, or convenience, even though these claims are accompanied by bibliographical references to randomised clinical trials published in reputable medical journals and seem to be evidence-based.'

Ref: *Pilar Villanueva, Salvador Peiró, Julián Librero et al.* Accuracy of pharmaceutical advertisements in medical journals. Lancet 2003; 361: 27-32

Text in full:
http://www.thelancet.com/journal/vol361/iss9351/full/llan.361.9351.original_research.23828.1

Lancet comment:
http://www.thelancet.com/journal/vol361/iss9351/full/llan.361.9351.editorial_and_review.23889.1

C O M M E N T

Recent proposals to broaden pharmaceutical advertising in Europe to patients were the focus of much debate, and were eventually not accepted. If, as results from this study suggest, regulation of claims for advertising is not even currently effective for medical professionals, this is one example that must cast doubt on industry claims to self-regulate future advertising to patients.

Lack of new drugs is reaching crisis point, says review

Roger Dobson, BMJ

The number of new drugs approved in the United States last year fell to half the annual average over the past five years. Only 15 new drugs were approved by the Food and Drug Administration in 2002, compared with a five year annual average of 31, says an editorial in Nature Reviews Drug Discovery (2003:2:3).

It warns that the fall in the number of new drugs is reaching crisis point and says that new drug applications are down worldwide.

It says that the European Parliament's environment committee has asked Thomas Lonngren, executive director of the European Agency for the Evaluation of Medicinal Products, to explain the fall in the number of applications.

"The miserable tally of new drug approvals in 2002 - at the time of writing, just 15 new molecular entities had passed FDA review, well down even on the depressingly low average for the last five years of 31 a year - shows just how rare an event success can be in the drug discovery world. And with new drug application numbers down worldwide, concern is beginning to spread beyond the borders of the pharmaceutical industry," says the editorial.

"Faced with sparsely populated pipelines, companies are beginning to shift research budgets towards more aggressive marketing of existing products. These are worrying times."

It points out that the process of turning ideas into drugs is acknowledged as being the hardest skill to teach new recruits to the drug discovery business.

And a report in the same journal (2003:2;63-9) says that selecting research targets for new drugs takes place in an environment that is strongly influenced by financial considerations.

It warns that most so-called blockbuster drugs were not forecast to be big sellers. The initial sales forecast for tamoxifen, it points out, was a modest £100,000 ($160,000; ¤150,000).

"To select a proposed research target, a range of issues needs to be evaluated. The first, and perhaps most important, is what constitutes an improved medicine. Many descriptors of varying utility are used to describe new medicines.

"The current favourite is `blockbuster drug,' which is much used by stock analysts to indicate annual sales in excess of US $1 billion." The authors say that most marketing departments did not forecast the success of these drugs at the time the decision was made to select the target.

The report adds, "Furthermore, if informal conversations are a reliable guide, several projects that resulted in multi-million pound sales were not strongly supported at the phase of target selection, even by the research manager. The point here is not to criticise those who prepare sales forecasts, but to emphasise the inherently unpredictable nature of sales forecasting, particularly for truly innovative medicines."

Source: BMJ 2003;326:119 (18 January)
http://bmj.com/cgi/content/full/326/7381/119

Medicines Control Agency must be more open

Zosia Kmietowicz, BMJ

The UK Medicines Control Agency needs to communicate better with the public about the safety of medicines and to become more transparent about the way it operates, says an independent review.

In its report, the National Audit Office has praised the agency for tackling financial pressures, human resources, and technology issues in a changing marketplace. The agency has seen a sharp downturn in the number of applications for innovative chemicals in the past five years, and its services to the public and the pharmaceutical industry have changed in that time from that of simply a licensing authority to an industry adviser and guardian of public health.

However, to fulfil its role of protecting the public, the agency needs to be more "outward looking" and produce information on the safety of medicines tailored directly to the public in a similar way to the Food and Drug Administration in the United States, says the report.

Many members of the public, and even some health professionals, do not understand the role of the agency, but as access to medicines becomes easier through the internet its role needs to be made much clearer. There is also "scope to improve" the transparency of the consultations that the agency has with patient groups and other stakeholders, says the report.

Although the agency is recognised for running a range of measures that ensure medicines are used safely and effectively, it is criticised in the report for not routinely checking that these warnings are being heeded. "There is some evidence that safety messages do not always get through to those who need them," says the report.

At the moment the agency funds itself through fees to the pharmaceutical industry, in stark contrast to similar organisations in other countries, which are largely funded through government money, notes the report. This may need to change in the future, and the Department of Health "may need to consider the financial sustainability of the current funding arrangements."

Source: BMJ 2003;326:119 (18 January)
http://bmj.com/cgi/content/full/326/7381/119/a

ON THE WEB

Conference abstracts and reports:

4th International Workshop on Adverse Drug Reactions and Lipodystrophy

The abstracts from the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, held this past September, 2002, in San Diego, are now on-line on the AEGIS website: http://www.aegis.org/conferences/4thLipo

Drug Development for Antiretroviral Therapies (DART) 2002

Report from this conference on new agents for treatment of HIV conveniently held in Florida in December 2002:

- Nucleoside Analogues (NA)
- Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI)
- Protease Inhibitors (PI)
- New drugs with unique sites of activity
- Differentiation of Ziagen and NNRTI skin reactions by patch testing

http://www.hivandhepatitis.com/2003icr/hivdart/main.html

40th Annual Meeting of the Infectious Diseases Society of America

Abstracts from this meeting held in Chicago in October 2002 are now available in pdf format at:

http://www.journals.uchicago.edu/CID/2002Abstracts.html

53rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD)

A 32-page report from HIVandHepatitis.com of selected studies from this conference held in November 2002 in Boston.

http://www.hivandhepatitis.com/2002conf/aasld53/main.html

Medscape links:

Access to Medcape articles requires a one-time free registration.

Recent research in HIV infection: Part 2

AIDS Read 12(12) 2002

Brian Boyle

Discussion of the prevention, diagnosis, and treatment of important coinfections, including herpes simplex virus (HSV), hepatitis B virus (HBV), and hepatitis C virus (HCV).

http://www.medscape.com/viewarticle/446811

Less expensive HIV test

AIDS Read 12(12) 2002

Researchers at the Johns Hopkins Bloomberg School of Public Health and the University of Zurich have developed a less expensive test for monitoring the progression of HIV infection during the early stages of disease.

http://www.mescape.com/viewarticle/446809

Is there a pipeline?

Infections in Medicine

Jeffrey P. Nadler, MD

Several experienced HIV specialists have lamented the dearth of new treatments in the pipeline. I've heard this from patients too. The exception is the buzz around T-20 (enfuvirtide). I want to briefly excerpt some information gleaned from many sources at the recent Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), the Infectious Diseases Society of America annual meeting, and the Barcelona AIDS conference to try to dispel the apparent pessimism. Of course, this is far from a comprehensive survey.

http://www.medscape.com/viewarticle/447231

AIDS

Increased risk of lipoatrophy under Stavudine in HIV-1-infected patients: results of a substudy from a comparative trial. Full text from AIDS:

http://www.medscape.com/viewarticle/447512

Multiple measures of HIV burden in blood and tissue are correlated with each other but not with clinical parameters in aviremic subjects

This study looked for levels of residual HIV DNA and RNA in blood and gut reservoirs in aviremic patients, assessed correlations among compartmental measurements of HIV burden, and evaluated association with clinical parameters.

Full text from AIDS:

http://www.medscape.com/viewarticle/446613

Newsletters and reports:

The Hopkins HIV Report - January 2003

Contents:

http://hopkins-aids.edu/publications/report/report_toc_03.html

The HIV/AIDS vaccine research effort: an update

By Chris Beyrer M.D., M.P.H.

http://hopkins-aids.edu/publications/report/jan03_3.html

Top papers of 2002 - John G. Bartlett, M.D.

Author's choice for the twelve most important HIV-related publications of 2002 that have direct clinical relevance:

http://hopkins-aids.edu/publications/report/jan03_5.html

Report from the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

By Joseph Cofrancesco Jr., M.D., M.P.H.

http://hopkins-aids.edu/publications/report/jan03_2.html

PRN Notebook – December 2002

December 2002 Vol. VII, No. 4

HIV superinfection and immune control: implications for vaccine development? - Todd Allen, DVM, PhD

Dendritic cells: immune activators of virus facilitators?

Melissa Pope, PhD

Determinants of mucosal HIV replication and shedding

Scott J. Brodie, DVM, PhD

http://www.prn.org/prn_nb_cntnt/current.htm

IAPAC December 2002 Journal

How club drugs make HIV more dangerous

Jan Swanson and Alan Cooper

Club drugs, or recreational drugs, have recently been associated with increased high-risk sexual behaviors that, in turn, may cause higher incidence of HIV/AIDS. And, there is increasing evidence that club drugs interact with highly active antiretroviral therapy. What role should physicians and allied healthcare professionals play?

http://www.thebody.com/iapac/dec02/club_drug.html

ICCAC Report: HIV grudgingly yields some secrets (or, orthography and the retrovirus)

Mark Mascolini

While many of HIV's dark mysteries remain tightly under wraps, the 42nd ICAAC yielded some clues to antiretroviral management. New studies focused on starting, stopping, and changing therapy - and on new antiretrovirals.

http://www.thebody.com/iapac/dec02/icaac.html

TAGline – November 2002

http://www.thebody.com/tag/tagix.html

SSITT downer? Nattering nabobs' noxious spin, and the imperiled future of STI research

"When an investigational drug causes a 0.4 log drop in viral load, it is evidence of biological activity. When the first large auto-vaccination study produces the same result, it signals the end of an entire field of HIV research."

Richard Jeffreys analyses the results from the Swiss-Spanish Intermittent Treatment Trial (SSITT) more optimistically than the lead investigators and argues for continued research in this area.

http://www.thebody.com/tag/nov02/altered_states.html

Research and policy recommendations for HIV/HCV coinfection

Critical recommendations from updated coinfection report, Version 2.0, February 2003.

(pdf format only)

http://www.aidsinfonyc.org/tag/comp/hcvResearch.pdf

IAVI Report - December 2002/January 2003

International AIDS Vaccine Initiative report now online:

- Clinical Trials Watch: Ongoing preventive trials of HIV vaccines
- Cent Gardes vaccine meeting highlights role of antibodies in protection
- GAVI partners assess progress on delivering today's vaccines to children
- Are babies in a blind spot?

A workshop in Seattle highlights the still-formidable barriers to clinical trials of vaccines in paediatric populations, which are at high risk of HIV infection via breastmilk in many areas of the world.

- Gathering of regulators from Southern Africa tackles vaccines and microbicides

Difficulties faced by representatives of regulatory agencies and institutional review boards in approving trials and licensing HIV vaccines and microbicides.

- Bringing vaccines to Soweto: An interview with Glenda Gray

A leader at one of Africa's premiere AIDS units and clinical research sites, Glenda Gray has been part of pioneering research, especially in the field of reducing mother-to-child transmission. Here, she discusses the team's recent expansion into vaccines and the challenges of involving young people in vaccine trials.

http://www.iavi.org/iavireport/

Co-infection:

Spanish guidelines on management of HIV coinfection with Hepatitis A, B and C

The Spanish AIDS Group GESIDA guidelines (written in English) on the management of patients coinfected with HIV and viral hepatitis that were first released in Barcelona in July 2002 are now on the web. These are the first comprehensive recommendations on HIV coinfection with viral hepatitis to appear from any credible medical organisation. Posted as a pdf file:

http://www.hivandhepatitis.com/hiv_hbv_co_inf.html

Think tank explores liver transplants in HIV/AIDS

amfAR convened a think tank of researchers and clinicians January 10–11, 2003, to discuss ongoing studies on the safety and efficacy of liver transplants in HIV-infected patients and to assess future research priorities. Report:

http://www.amfar.org/cgi-bin/iowa/programs/researchc/record.html?record=194

Organ Transplants for HIV+ Patients:

http://www.amfar.org/cgi-bin/iowa/programs/researchc/record.html?record=184

Report by Larry Kramer:

http://www.hivandhepatitis.com/recent/transplantation/

Other links:

In HIV vaccine efforts, new strategies and patience are needed in equal measure

Joan Stephenson, PhD

On the one hand, with 40 million people infected worldwide with HIV and the number growing by some 15,000 newly infected individuals each day, the need for a vaccine has never been more urgent. On the other hand, there are a number of hurdles that have made HIV vaccine research a painfully slow process that demands patience as well as perseverance.

http://jama.ama-assn.org/issues/v288n21/ffull/jmn1204-1.html

Treatment issues for women

By Angela Garcia, Jennifer McGaugh, Heidi Nass, Cathy Olufs and Claire Rappoport

If you are a woman living with HIV, you probably have a lot of questions. We all do. Since the first studies focusing on positive women began in 1994, many treatment advances have been made. But there are still few sources of treatment information and support for positive women. Many questions remain unanswered about how HIV and treatments for HIV may affect women differently.

Sections include:
Hormones and HIV, Anaemia, Gut health, Muscle mass, Lipodystrophy, Bone health, GYN care, Period problems, Yeast infections, Herpes, Genital tract infections, HPV and cervical dysplasia, Anal HPV and anal dysplasia, Conclusion and Resource list.
http://www.thebody.com/cria/women/contents.html

Depression and HIV

Leaflet from the US National Institute of Mental Health about this important and often overlooked aspect of HIV.

http://www.thebody.com/nimh/depression_hiv.html

011703a.html

Resistance algorithms updated

The French virology group within the ANRS (AC11) that works on resistance, has just updated its algorithm table on which mutation confers viral resistance. The update is done twice a year.

http://www.hivfrenchresistance.org

PUBLICATIONS AND SERVICES FROM i-BASE

Portuguese translation of 'Introduction to Combination Therapy':

Introdução à Terapêutica de Combinação

This essential non-technical patient guide to combination therapy has now been translated into Portuguese. It is available to download as a pdf file and reprint free from the i-Base website:

http://www.i-base.info/pdf/guides/nonuk/COMBO_PORTUGUESE_jan03.pdf

Printed versions of this booklet are also available in English, French, Italian, Spanish, Chinese, and Macedonian. It explains what combination therapy is, how well it works, who can benefit from it, when to start taking it, some differences between treating men and women, side effects, the best combinations, changing treatment, taking part in drug trials, your relationship with your doctor, the importance of adherence, and drug resistance and how to avoid it. To order copies, see below

Changing Treatment: a guide to second-line and salvage therapy

Updated January 2003. These treatment guides are reviewed every six months to ensure the latest information is available. Many factors contribute to whether a combination works and in salvage therapy it is important to look at all of these together.

The section on treatment strategies has been rewritten and updated and includes a new section on viral fitness and alternating treatment regimens. The information on expanded access and experimental treatments has also been updated.

Since the previous edition several new treatments have become available to use in salvage therapy and these are also included in the guide:

• T-20 has reported clear benefits for people resistant to current drugs - marketing approval is expected in mid 2003 and prior to this it will be available in a limited expanded access programme from early 2003.

• Atazanavir appears to increase cholesterol and triglycerides less than other PIs and is available in an expanded access programme for people with raised lipids on current PIs.

• Tipranavir, a PI with activity against currently resistant HIV, will be available during 2003 in a limited emergency access programme.

For additional free copies, including bulk orders see below

UK-Community Advisory Board reports and presentations

The UK-Community Advisory Board (UK-CAB) was set up by HIV i-Base last year as a network for community treatment workers across the UK and has so far held three meetings. Each meeting includes two training lectures and a meeting with a pharmaceutical company.

The programme, reading material and powerpoint slides from the presentations to the fourth meeting held on 31 January 2003 are now posted to the i-Base website. This meeting focused on gender issues and HIV, and also on hepatitis and coinfection.

http://www.i-base.info/ukcab/jan03/index.html

Transcriptions and slides of training sessions from previous meetings also on the site include:

Genetics, resistance and HIV – by Professor Clive Loveday

Approaches to Salvage Therapy – by Dr Mike Youle

Pregnancy, HIV and Women's Health - by Dr Karen Beckerman

Fertility treatment and sperm-washing techniques – by Dr Leila Frodsham

http://www.i-base.info/education/index.html

Guide to Avoiding and Managing Side Effects

A comprehensive 36-page guide that is aimed at helping anyone using HIV drugs to get the most out of their treatment, the most out of their relationships with their doctor and other health professionals, to get better medical care to improve their health and, most importantly, to enjoy a better quality of life.

It is written by people who are HIV-positive, who have been on most of the treatments, who have had many of the side effects and who have learnt to negotiate their own healthcare.

French, Spanish and Chinese translations of this booklet are also available. To order copies, see below.

Positive Treatment News (PTN)

The latest issue of Positive Treatment News, our magazine for positive people, looks at adherence (missed any pills recently, need any advice?), the latest information about side effects and treatments, and the benefits and risks of joining a drug trial or study.

There is also a detailed look at weight loss and what can be done about it, the official treatment guidelines, salvage therapy and treatment information provision for the African community. To order copies, see below.

HIV Treatment Bulletin (HTB)

This is the journal you are reading now; a review of the latest research and other news in the field. HTB is published 10 times a year on our website (http://www.i-base.info) and in a printed version. The printed version is available at most HIV clinics in

the UK and is available free by post: see below for details.

Treatment information request service

i-Base offers specialised treatment information for individuals, based on the latest research.

We can provide information and advice over the phone, and we can also mail or email copies of the latest research studies relevant to the caller.

For details call the i-Base treatment information free phone line on 0808 800 6013. The line is usually staffed by positive people and is open Mondays, Tuesdays and Wednesday from 12 noon to 4pm.

All calls are in confidence and are free within the UK.

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http://www.i-base.info

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Introduction to Combination Therapy *(August 2002)*
IN ENGLISH

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Changing Treatment - Guide to Second-line and Salvage Therapy *(April 2002)*

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Positive Treatment News (PTN) *from Spring 2003*

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Paediatric HIV Care - March 2001 - Report from i-Base Paediatric Meeting

1 ☐ 5 ☐ 10 ☐ Other_____ _____ _____

Adherence planners and side effect diary sheets - In pads of 50 sheets for adherence support

1 ☐ 5 ☐ 10 ☐ Other_____ _____ _____

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