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EDITORIAL

Perhaps it is inevitable, with the number of governments involved in the Global Fund to Fight AIDS, TB and Malaria, with the amounts of money involved, and the nature of the work it has been set up to finance, that there should be high emotions and low politics surrounding the fund, as we report this issue.

The good news is that many nations – and a few organisations - have made substantial contributions to the fund, and as world leaders gathered for the G8 summit in June some of those donations were increased; and there will be a conference in Paris in July to find ways to raise more money. To keep track of who's doing what, this month we publish a full list of donors.

The bad news is that, quite simply, the Global Fund has far too little money.

HIV Treatment Bulletin believes that it is not only important for a publication such as this to report on the latest scientific developments, but also to pursue matters relating to access to treatments. The next big political issue in this context will come in the run up to the World Trade Organisation meeting in September which will decide how to balance the conflicting interests of multinational pharmaceutical companies that are keen to hold on to their patents, and generic producers that are able to provide more medicine for less money. But access to treatments is not only about money and politics: we also report on new research from South Africa that shows that adherence is not a barrier to successful therapy in a resource-poor setting.

For those with access to treatment, long term cardiovascular risk is clearly a real concern. The preliminary results from D:A:D – the largest study to look prospectively at increased risk - repay close assessment, and are also reported in this issue.

Included with this mailing of HTB is a small pocket-sized booklet to keep a record of an individual treatment history. We hope that this will not only be used by newly diagnosed people to help understand their own health, but also by those who have been HIV-positive for many years – and that clinicians will find this of benefit for their patients.

As with all i-Base material, these booklets are available free, including in bulk to clinics – please use the separate enclosed fax-back form to order them, or the back page of HTB if ordering other publications at the same time.

The next issue of HTB will be a double issue for August/September and be distributed mid-August for holiday reading... This will enable us to include reports from the 5th Lipodystrophy Workshop and 2nd IAS Conference – both in Paris in July - and the 12th Resistance Workshop in Mexico.

TREATMENT ACCESS

Activist anger over US 'ambush' of the Global Fund

Graham McKerrow, HIV i-Base

The Group of Eight most industrialised nations (G8) and the Global Fund to fight HIV, TB and Malaria have announced new donations by rich countries to the fund – but there is widespread criticism that the donations are far too small, and one activist group says an American "ambush" will divert money to bilateral agreements between donor countries and developing countries and leave the fund impotent.

The G8 summit in the French Alpine town of Evian in early June was criticised for the limited pledges of new money for the fund. Amid much rhetoric, The European Union promised to consider, at its own summit in Salonika, Greece on 26 June, matching the $1 billion promised by the United States. This is part of a much larger sum, $15 billion over five years, that George Bush has said the US will give in bilateral aid directly to selected countries. The G8 and the Global Fund have also agreed to hold a conference, in Paris in July, to bring together governments and other organisations to plan a strategy for further fund raising for the Global Fund.

President Jacques Chirac told the G8 meeting that France would triple its donation to the Global Fund from 50m euros to 150m euros ($175 million) annually up to 2006. The week before the summit, Tony Blair announced that the UK's contribution would be increased from $200 million to $280 million up to 2008.

Chirac said Bush was "totally right" to urge other countries to match the US contribution and thought Europe would "accept the challenge." The French president also said he was in favour of a tax on the arms trade to help finance a global fund to feed the world's hungry. Such a tax, suggested by Brazilian President Luiz Inacio Lula da Silva, "would not be at all unjustified," Chirac told a press conference.

Jose-Maria Zuniga, president and CEO of the International Association of Physicians in AIDS Care, commented: "With President Bush's recent commitment of his government's resources to stepping up this battle, the onus was placed on the world's other wealthy countries to show equal commitment and to demonstrate the need for the United States to live up to the authorisations approved by President Bush. This is a role and responsibility that, with the notable exceptions of France and the United Kingdom, other G8 nations are now failing to live up to. In fact, several other non-G8 nations continue to surpass these wealthier states in living up to their proportional responsibilities."

European Commission president Romano Prodi questioned how much of President Bush's $15 billion would actually materialise, pointing out the money still had to be approved by Congress. "The money's not on the table," Prodi told reporters. He also dampened speculation that the EU would give $1 billion to match the US donation to the Global Fund, saying European Union payments to the fund remained higher than Washington's.

"It was really easy for me to match it, it's certainly not a problem because we are giving more than that [already]," Prodi said.

At the end of May Richard Feacham, executive director of the Global Fund, told the French newspaper Le Monde that the fund needed $4 billion by the end of 2004. But by the time he reported to the fund's board meeting in Geneva on 5 June the amount yet to be raised by the end of next year had fallen to $3 billion. Feacham reported that pledges to the fund had increased by $1.2 billion in one week: France promised 450 million euros, the European Commission promised 340 million euros, Italy 200 million euros and the UK an extra $80 million. However, these promises cover different periods going up to 2008 and only 23% of the fund's needs up to the end of 2004 are met by these pledges.

Feacham said that because the US promise of $1 billion was conditional on twice that sum being raised from other sources, he hoped the EU would provide $1 billion and that public and private donors outside the US and Europe would provide another $1 billion.

A statement issued by the fund said: "The most urgent need for resources is the Global Fund's third round of proposals [to be considered in October]. Over 200 proposals have been received from 85 countries, requesting $2 billion for two years. It is likely that at least half of these requests will be recommended to the board for approval in October, but the Fund has only $400 million in remaining pledges for 2003. Needs for 2004 include two more proposal rounds."

Activists reacted angrily to this shortage of cash, and to moves to limit the demand for money from the fund rather than attempts to raise more money. Paul Davis of Health GAP (Global Access Project) emailed activists saying the USA had "ambushed" the fund at its board meeting.

Davis described the "ambush" thus: "The US has decided to put everything into its bilateral AIDS programme. Therefore, it is working hard to reduce all the countries' obligations to pay into the Global Fund, and by manipulating the agenda through control of the Chair, Tommy Thompson [the US health secretary] arranged a new policy to reject any Global Fund application for round 3 beyond the $417 million now in the bank. Deviously, a policy was adopted that almost no one understood. That means that only $417 million of the $2 billion in grants [applications] that just came in will be funded, in spite of ample cash in the bank by the time that cheques would have to be written. The board may now only approve good applications up to the amount of pledges in 2003.

"What this means is that the $1-1.5 billion the Global Fund is fairly certain to have pledged by the October board meeting simply does not count, because most of those cheques will be written in 2004. So most of the applications are to be rejected. This policy reduces pressure on the donors, since they will not have unfunded but approved proposals laying around."

To date, the Global Fund has considered two proposal rounds, approving US$ 1.5 billion to 93 countries over two years. (See table for details of pledges and contributions to the fund up to the end of May.)

The G8 meeting contained further disappointment in its six-point so-called Action Plan in which the G8 repeatedly use phrases like "we express our continued concern…" and "reiterate our commitment to fight AIDS, as well as TB and Malaria, as agreed in Okinawa…" A section on access to medicines welcomed and encouraged pharmaceutical companies' decisions to supply free and discounted drugs to developing countries, but it made no mention of the important role the supply of generic medicines plays in cutting prices and increasing distribution of antiretrovirals. A very woolly paragraph instructed G8 ministers and officials to work with partners in the World Trade Organisation to "establish a multilateral solution in the WTO" to the problems faced when developing countries import from other developing countries medicines produced under compulsory licence for addressing public health crises.

Before the summit, Medecins Sans Frontieres demanded that the G8 make existing essential medicines affordable to those who need them by supporting an equitable pricing system based on generic competition, and abandon reliance on voluntary, ad hoc efforts to increase access to medicines, "which do more to protect the interests of the pharmaceutical industry than the lives of people in developing countries".

MSF also called on the G8 to ensure that public health needs were prioritised over commercial interests in international trade negotiations so that patents no longer constituted a barrier to access to medicines.

Global Fund to Fight AIDS, TB and Malaria

DONORSTOTAL PLEDGES TO DATE

	PLEDGE IN ORIGINAL CURRENCY(if other than USD)	PLEDGE VALUE IN USD	PERIOD OF PLEDGE (blank if unknown)
GFATM Trust Account (at World Bank)			
Andorra		100,000	2002
Austria	EUR 1 ,000,000	1,075,900	2002
Belgium	EUR 18,000,000	19,283,079	2001-2003
Burkina Faso		75,000	2002
Cameroon		100,000	2003
Canada		100,000,000	2002-2005
Denmark	DKK 110,000,000	14,816,511	2002
European Commission	EUR 120,000,000	137,064,385	2001-2002
France	EUR 150,000,000	172,811,060	2002-2004
Gates Foundation		100,000,000	2002-2003
Germany	EUR 200,000,000	228,585,062	2002-2006
Ireland	EUR 12,900,000	12,982,660	2002-2003
Italy		200,000,000	2002-2003
Japan		200,000,000	2002-2004
Kenya	KES 653,550	8,273	2001
Kuwait		1,000,000	2003
Liberia		25,000	
Liechtenstein		100,000	2002
Luxembourg	EUR 3,000,000	3,284,394	2002-2004
Monaco		44,000	2002
Netherlands	EUR 135,000,000	154,423,648	2002-2005
New Zealand	NZD 1,250,000	694,444	2003
Niger		50,000	
Nigeria		10,000,000	2002-
Norway	NOK 130,000,000	17,962,003	2002
Poland		10,000	2003
Russia		20,000,000	2002-2006
Rwanda		1,000,000	
Saudi Arabia		10,000,000	2003-2006
Spain		50,000,000	2003-2004
Sweden	SEK 600,000,000	69,872,734	2002-2004
Switzerland		10,000,000	2002-2003
Thailand		5,000,000	2003-2007
Uganda		2,000,000	
United Kingdom	GBP 138,000,000	218,342,667	2001-2005
United States		1,650,000,000	2001-2008
Zambia	ZMK 83,500,000	25,000	2002
Zimbabwe		1,000,000	
Total via World Bank		**3,411,735,820**	
UN Foundation Trust Account			
Individuals, Groups & Events			
Mr. Kofi Annan		100,000	2001
Amb. D. Fernandez		100,000	2001
People of Taiwan		1,000,000	2002
Real Madrid Soccer Match		112,487	2002
Other		273,565	2002-2003
Corporate			
Eni S.p.A.		500,000	2002
Statoil		100,000	2003
Winterthur		1,000,000	2002
Other		17,910	2002-2003
Foundations, Non-profits and NGO's			
Int'l Olympic Committee		100,000	2001
Other		40,802	2002-2003
Total via UN Foundation		**3,344,764**	
Total		**3,415,080,584**	

Notes:

1 (a) For pledges made in currencies other than US dollars, the pledge amount in USD comprises the actual USD value realised from any contributions made plus the USD equivalent of the remainder of the pledge calculated using UN operational rates of exchange at 1 May 2003 (15 May 2003 for Euro pledges).

(b) Where pledges have not been specified for individual years, the amount shown as pledged for a period is the sum of contributions received in that period.

2 Contributions in process comprise amounts remitted to holding accounts with the Trustee pending execution of contribution agreements and amounts expected to be received within one month pursuant to a signed contribution agreement.

3 Contributions from the Gates Foundation are received via the GFATM Trust account.

4 Payments in process for 2002: Kenya (8,273) and Zambia (25,000).

Links:

Global Fund to Fight AIDS, TB and Malaria

http://www.globalfundATM.org/

Fund the Fund

http://www.fundthefund.org/

Global Fund Observer

http://www.aidspan.org/gfo/

Letter from Kofi Annan to the G8

http://allafrica.com/stories/200305300078.html

Medecins Sans Frontieres

http://www.msf.org/

Health GAP (Global Access Project)

http://www.healthgap.org/

European Union

http://europa.eu.int/

European Commission

http://europa.eu.int/comm/

University of Toronto G8 Information Centre

http://www.g7.utoronto.ca/

International Association of Physicians in AIDS Care

http://www.iapac.org/

Global Fund requires 'significant' new money, and other reports from HTB 4,5 see under Treatment Access at

http://www.i-base.info/pub/htb/v4/htb4-5/index.html

$15 billion AIDS bill signed, but full funding shaky

President George Bush signed landmark legislation authorising $15 billion to fight AIDS in Africa and the Caribbean, and now the spotlight switches to making sure Congress' notoriously independent-minded appropriators actually come up with the money.

Bush signed the bill in a State Department ceremony, flanked by ambassadors from the 14 nations that are the focus of the AIDS effort. The bill calls for $3 billion a year over five years, almost tripling the amount of money the United States has spent to prevent and treat HIV and AIDS in those countries.

But getting the money during a federal budget crunch could be tough. "The devil is really in the details. Between the tax cuts and all the money being spent on terrorism, there's little discretionary money left," said Fred Dillon, policy director for the San Francisco-based Pangaea Global AIDS Foundation. "It will be extremely difficult."

Bush, who has surprised and pleased AIDS activists with the commitment he has shown to combating the global pandemic since unveiling his initiative in his State of the Union address in January, didn't specifically commit himself to a full appropriation in the expanded programme's first year.

But he said, "We'll provide unprecedented resources to the effort. And we will keep our commitment until we have turned the tide against AIDS."

Some of Bush's usual critics have already stepped forward to press him to force the Congress controlled by his fellow Republicans to come through with the full appropriation. The President originally proposed starting the programme slowly, at about $1.7 billion in the first year, then increasing the spending over five years. But Congress authorised $3 billion a year.

"I am tired of lofty rhetoric that makes people feel good but bears little resemblance to the administration's actions," Senator Patrick Leahy (Democrat, Vermont) said on the Senate floor last Friday. "The President should do what he says. He should do what he is asking others to do, and submit a budget amendment for the $3 billion authorised to fight AIDS."

Representative Barbara Lee (Democrat, Oakland), who has been pushing for more AIDS funding for years, said, "I have to be cautiously optimistic. I think it would be morally wrong to move this bill and raise the hopes of millions who are dying of this

pandemic and then not come through."

Representative Dave Weldon (Republican, Florida), a physician who has treated AIDS patients and is a House Appropriations Committee member, said momentum was with the global AIDS bill's backers.

"With the vote we had on this," he said, referring to the bill's overwhelming margin of passage, "it will be hard for us not to address the requirements of this legislation."

Mark Isaac, vice president of the Elizabeth Glaser Paediatric AIDS Foundation, praised Bush's commitment, but added, "We need to hold his feet and the Congress' feet to the fire."

Bill O'Keefe, director of government relations at Catholic Relief Services, which operates HIV-AIDS programmes in 31 foreign countries, said that with Republicans in charge in Washington, AIDS funding would be a test for Bush.

"With the House and Senate under Republican control, the administration will have an opportunity to demonstrate its commitment," O'Keefe said. "We hope the President's will and commitment will be brought to bear."

The President said the legislation would prevent seven million infections, care for 10 million people with HIV and AIDS orphans and give anti-retroviral therapy to two million. The bill recommends that 55% of the money go to treatment, 20% to prevention, 15% to palliative care and 10% for orphans.

Source:

http://ww2.aegis.org/news/sc/2003/SC030524.html

New GAA report: US and G8 must act fast to rescue Global Fund

As President Bush signed a new global AIDS bill, the Global AIDS Alliance released a new report that details how the President's spending proposals will make the bill almost impossible to implement. The report calls on the President to immediately change course to avert a major shortfall in AIDS funding.

The bill, to be signed today in a White House ceremony, is the United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act of 2003. The bill recommends (but does not mandate) $3 billion in spending on global AIDS programmes in 2004, with up to $1 billion of that for the Global Fund to Fight AIDS, TB and Malaria.

But the President's actual spending proposal for direct AIDS programmes comes to only about half that amount ($1.7 billion), and cuts other programmes that assist the poorest countries. The President's spending plan, already approved by Congress, envisions not reaching the level specified in the bill until 2006. In addition, the President has asked the Congress to provide only 5% of what the Global Fund says it needs in additional resources for 2004.

"The President wants concerned Americans to believe he is backing an emergency plan to fight AIDS," noted Dr Paul Zeitz, executive director of the Global AIDS Alliance. "But, his actual plan fails to fund what Congress clearly regards as a more realistic and balanced approach, given the scale of the epidemic. The President should sponsor an amendment to the Budget to allow for the needed additional spending on AIDS as well as other programmes that help poor countries."

At a minimum, the Fund will need to spend $42 billion over the years 2002 to 2008, but there is little evidence donors are preparing to provide such contributions.

The report aims harsh criticism at other G7 members for failing to provide appropriate contributions to the Fund. Plus, other relatively wealthy governments outside the G7, including Australia and Portugal, have failed to donate at all, despite having the means to do so.

The G8 meeting and the subsequent Donors Conference in Paris on 16 July are vitally important upcoming opportunities for the US, the Europeans and others to show the level of commitment desperately needed.

The full 12-page Global AIDS Alliance report can be downloaded at:

http://www.globalaidsalliance.org/fundreport.html

Source: Global AIDS Alliance

Contact: David Bryden of Global AIDS Alliance, +1-202-549-3664

Link:

http://www.globalaidsalliance.org/

World Health Assembly approves resolution supporting public health considerations in drug policy

The World Health Assembly, the governing body of the World Health Organisation, has approved a resolution stating that countries and pharmaceutical companies should consider public health factors when making policies on access to drugs, including antiretroviral medications. The resolution, sponsored by Brazil, addresses concerns from the pharmaceutical industry by encouraging research and development of new drugs and by recognising intellectual property rights. The Brazilian delegates engaged in "difficult negotiations" with US delegates, who had submitted a different draft resolution focusing on the defence of patents and intellectual property law. Brazil threatened to submit its own proposal for a vote and rejected attempts to combine the resolutions. The draft resolution was co-sponsored by the African bloc, Peru, Bolivia, Ecuador, Thailand and Indonesia and was supported by the European nations. The resolution calls on countries to reach a consensus on generic drugs before the September ministerial meeting of the World Trade Organisation.

Talks stalled last year

WTO talks in Geneva over generic drug access have been stalled since members missed a 31 December 2002 deadline to reach an agreement. In February, US negotiators refused to sign a deal under the Doha declaration to allow developing nations to override patent protections to produce generic versions of drugs to combat public health epidemics unless wording was included to specify which diseases constituted a public health epidemic. The United States said that without such a list, developing nations could use patent overrides to produce generic versions of any patented drug — such as Viagra — that is not used to fight public health epidemics. Brazil, which is considered to be a pioneer in AIDS policy, was asked to assist WHO in the development of the agency's five-year antiretroviral treatment strategy.

Links:

World Health Organisation
http://www.who.int/en/

World Trade Organisation
http://www.wto.org/

Doha Declaration
http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_e.htm

Related Kaiser Daily HIV/AIDS Reports
http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=1&DR_ID=16938

http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=1&DR_ID=17833

WHO Assembly analysis

Brook K Baker, Health GAP

Now that the dust has settled at the 56th World Health Assembly (WHA), it might be useful to analyse what if any progress is likely at the World Health Organisation (WHO) in the battle against HIV/AIDS. Others may certainly have things to add (or to disagree with), but here's my take on the Assembly.

A full commitment to three million by 2005

The most promising outcome of the Assembly was the statement by the newly elected Director-General, JW Lee, that he "committed" the WHO to achieving the Barcelona goal of "three by five", or three million people living with HIV/AIDS in developing countries put onto antiretroviral treatment by the end of 2005.

Although the written version of his prepared remarks were less direct ("I will ensure that WHO provides leadership toward the bold "three-by-five" target"), his speech, by my memory anyway, was more concrete. This goal, of course, cannot be reached without adequate financing, a matter of some desperation at this point given the near bankruptcy of the Global Fund.

However, it also cannot be reached unless there is a sea change in the planning process whereby developing countries get "technical assistance" on utilising all existing programmatic capacity on HIV/AIDS treatment, care, and prevention and further technical assistance on capacity building within the health care sector. (It is interesting to note that in the passed resolution, the World Health Assembly backed away from "endorsing" the three-by-five goal and instead is "bearing it in mind" the weak will and scepticism of some European countries.)

In its report on "WHO's contribution to the follow-up of the United Nations General Assembly special session on HIV/AIDS," the Secretariat stated that:

"WHO is working with an international coalition of partners to draft and implement a plan of action for extending access to ARV treatments to three million people by 2005. The plan will include technical assistance and information sharing to guide countries in implementing national treatment programmes." (Paragraph 16.)

Health GAP and other activists at the WHA urged the Director General to issue this plan as soon as possible, hopefully by the September United Nations review of the UNGASS (United Nations General Assembly Special Session on HIV/AIDS) Declaration of Commitment. Despite the value of a global plan, however, the real test of the WHO's newfound commitment to three-by-five will be the technical assistance it provides on the ground in individual countries to national health ministries and other stakeholders. As many know, Health GAP considers the lack of technical assistance concerning scale-up and capacity building to be a key obstacle to the realisation of universal access to treatment by 2010 (50% coverage by 2005 and an additional 10% each year thereafter). Fortunately, the Director General is committed to bringing in new staff that will collaborate with health ministries and others to customise scale-up and capacity building plans to local circumstances. This will be challenging work, but the Secretariat actually envisions much less work in Geneva and much more work in country, calling this initiative a "commitment to results at the country level." In support of this approach, the Assembly, in its Resolution on a Global Health Sector Strategy for HIV/AIDS, passed a provision which requests that the Director-General "support, mobilise, and facilitate efforts of Member States and other concerned parties" to achieve the three-by-five goal.

Funding the Global Fund and technical assistance to Country Coordinating Mechanisms - mixed success

Health GAP, Act Up Paris, and other Fund-The-Fund allies had a goal of getting the Assembly to endorse a dues-based commitment to full funding of the Global Fund to Fight AIDS, TB and Malaria, but activists were not successful in getting explicit language to that effect. Instead, there is a veiled reference in the final HIV/AIDS resolution: Member States are exhorted, as a matter of urgency, "to take all necessary steps, including the mobilisation of resources, to fulfil their obligation under the [UNGASS Declaration of Commitment]."

Since the UNGASS Declaration had acknowledged the need for funding levels of $7-10 billion for HIV/AIDS alone by 2005, and since those numbers have been expanding, based on more precise calculations and on the inclusion of capacity building goals and coverage of TB and malaria (eg WHO Commission on Macroeconomics and Health), the context of this statement is clear - the global fight against HIV/AIDS is still grossly underfunded, particularly at the Global Fund which has virtually no resources to commit to an estimated $1.6 billion of new, high quality proposals expected in round three (due date 31 May).

Another way to energise the Global Fund and to demonstrate the extent of unmet need and capacity is for developing countries to become bolder in submitting robust treatment proposals to the Global Fund whereby they request scale-up and capacity building in a much more dynamic way. Countries have been discouraged from doing so so far because of persistent underfunding of the Global Fund, first by the US and then by other rich donors. When subtle messages weren't enough, donor representatives forced countries like Malawi to reduce the scale of their treatment proposals. And, of course, developing countries face their own crises of political commitment to AIDS treatment, especially given the uncertain sustainability of treatment programs initiated with Global Fund dollars.

To try to counteract this downward cycle of reduced expectations and suppressed demand, Health GAP and others have been trying to force the Global Fund to clarify that well-rounded proposals should ordinarily include robust treatment plans. Health GAP has also urged that developing countries' Country Coordinating Mechanisms (CCMs) received technical assistance on crafting high quality treatment-focused proposals. Thus, in addition to providing technical assistance on capacity utilisation and expansion, the WHO's AIDS Strategy Resolution also addresses helping CCMs file robust proposals to the Global Fund. Health GAP had urged the Secretariat to be proactive in providing technical assistance to CCMs, but the conservative politics at the Assembly resulted in a resolution that conditions technical assistance on countries asking for it. Hopefully the message will get out to countries that they can't not ask.

Pre-qualification

Health GAP, Health Action International (HAI) and others at the Assembly argued that the WHO's drug pre-qualification system should be strengthened and extended.

Unfortunately, there was no formal resolution on the Medicines Policy and activists were unsuccessful in getting a statement on pre-qualification squeezed into the AIDS Strategy Resolution. Nonetheless, the importance of enhancing the pre-qualification process, of adding resources, and of providing more pro-active assistance regarding registration of generics, including those with fixed dose combination, was discussed informally with the secretariat and was raised from the floor during the medicines policy debate. However, this programme, critical to the fast-track registration of generic ARVs in developing countries, is crucial and its progress should be carefully monitored.

Access to medicines - prioritising health over intellectual property

The last major issue at the WHA, from a treatment access perspective, was the "Report by the secretariat on intellectual property rights (IPR), innovation, and public health." As Jamie Love has already reported, this was a pretty disappointing

document both with respect to product innovation and with respect to access to medicines. Fortunately, Brazil and other developing countries became active at the Assembly, with constructive intervention from NGOs, in developing a resolution for submission to the General Assembly. The US badly miscalculated its hand and submitted a truly brutal proposal that championed the expansion of intellectual property rights as the only mechanism for spurring innovation. The US went so far as to ignore the adoption of the Doha Declaration on the TRIPS (Trade-Related Aspects of Intellectual Property Rights) Agreement and Public Health, and thus was condemned publicly and privately for its IPR hubris.

In the end, the resolution that passed: (1) reaffirmed "that public health interests are paramount in both pharmaceutical and health policies," (2) urged Members states "to consider, whenever necessary, adapting national legislation in order to use to the full the flexibilities contained in [TRIPS]," (3) urged Member states to "maintain efforts aimed at reaching, within the WTO and before the fifth WTO Ministerial Conference, a consensus solution for paragraph six of the Doha Declaration, with a view to meeting the needs of the developing countries," (4) requesting the Director-General to support member states in the exchange and transfer of technology, especially with respect to antiretrovirals and other medicines to control tuberculosis, malaria, and other major health problems, and (5) to cooperate with member states, at their request, in monitoring and analysing the pharmaceutical and public health implication of relevant international agreements, including trade agreements.

In this regard, it is also useful to note that China succeeded in inserting two access to medicines provisions in the AIDS Strategy Resolution: (1) reaffirming that public health is paramount in both pharmaceutical and health policies and recognising difficulties developing countries have utilising compulsory licenses and, when necessary, using flexibilities in TRIPS to access medicines against HIV/AIDS and (2) urging the Director-General to mobilise support of actions taken by countries with an AIDS epidemic to obtain affordable and accessible drugs to combat HIV/AIDS.

With respect to IPR issues, the IP and AIDS Strategy Resolutions as passed contained three major deficits. First, the Resolutions did not directly encourage the Director-General to continue to intervene in WTO negotiations from a pro-public health perspective, especially concerning the desirability of utilising an Article 30 solution for the production-for-export problem. Given the rambling attack by the US from the floor about the WHO's intervention to the TRIPS Council on 17 September 2002, it is obvious how important such interventions might be in crystalising the best response to paragraph six problems. Second, the resolutions did not directly address the obligation of the WHO to monitor bilateral and regional trade agreements and to provide technical assistance to developing member states about avoiding TRIPS- and Doha-plus intellectual property protections. This issue is referenced in paragraph 19 of the secretariat's IP Report where it acknowledges that bilateral and regional trade agreements frequently fail to reflect the need for special treatment for health-related products. Finally, Health GAP and other activists had requested that the WHO provide technical assistance to developing countries concerning revision of their intellectual property laws to make maximum use of the flexibility in the TRIPS Agreement and in the Doha Declaration. At present, WIPO and USAID provide "Trojan-horse" technical assistance that is strongly biased towards enhanced, TRIPS-plus IP protection. To counteract this disabling assistance, the WHO should beef-up its capacity to provide concrete technical assistance on national IP reform (including roll-back of premature TRIPS compliance or of TRIPS-plus legislation) and on strategies for issuing compulsory licenses on essential AIDS medicines.

Obviously, the intellectual property debate is the most highly political and contentious area of policy for the WHO in its battle against the AIDS pandemic. No one would gladly get in a fight with the US and with Big Pharma on these issues because they fight long and dirty to maximise pharmaceutical hegemony for patent holders. However, activists will need to continue to place pressure on the WHO to assist people living with HIV/AIDS in their long struggle to access affordable medicines, which increasingly means accessing low cost, quality generics, whether produced locally or imported. Intellectual property is at the centre of this conundrum, and it must continue to be addressed by the WHO and others.

Bill Gates to give $1 million to Brazil's AIDS programme

Billionaire Microsoft founder Bill Gates will donate one million dollars to Brazil's fight against AIDS, the Bill and Melinda Gates Foundation announced Wednesday.

The donation, it said, will be in the form of the "Gates Prize for 2003 World Health," to be presented on Thursday to Dr. Paulo R. Teixeira, head of the Brazilian AIDS program.

Teixeira said the money would be disbursed among several centres that treat AIDS and care for orphans of the incurable disease.

Source:

http://www.aegis.org/

Adherence is not a barrier to successful antiretroviral therapy in South Africa

Polly Clayden, HIV i-Base

It is a widely held assumption that people in resource poor settings will be unable to be adherent to antiretroviral therapy, providing yet another barrier to their access to medicines essential to their care. A paper published in AIDS reports findings from an investigation designed to measure adherence in a cohort of semi-urban South Africans living in extreme poverty.

A total of 289 drug naïve patients were enrolled into this multi centre study recruited from the Cape Town AIDS Cohort receiving ART through phase III trials between January 1996 and May 2001.

All participants were ARV naïve and provided written consent to participate in the trials. Single group education sessions (generally in English) were conducted prior to the consenting process and study entry. No dedicated adherence counselling services, structured treatment support or formal adherence interventions were provided as part of the protocol. There were no off site visits by health care staff.

Patients in two studies in 1996 received dual therapy with an additional concurrent placebo controlled and double blinded drug (placebo vs NNRTI). In four other studies patients received triple therapy. PI containing regimens were used by 120 (41.5%) patients, NNRTI containing by 94 (32.5%), 30 (10.4%) took triple nucleoside regimens and 45 (15.6%) who initiated therapy in 1996 received dual nucleoside therapy. Regimens of 10 tablets or more per day were used by 55% of the cohort and 41% of regimens had some dietary restrictions.

Adherence to ART was determined over 48 weeks by counting tablet returns. Clinic visits were booked in multiples of 28 days and tablets usually dispensed in multiples of 30. Patients were asked to return all medication bottles and unused pills at each visit.

Logistic regression models including age, WHO clinical stage, home language, socio-economic status, baseline CD4 and viral load, complexity and type of regimen were recorded to determine predictors of incomplete adherence and virologic failure at 48 weeks.

The mean age of the cohort at initiation of therapy was 33.4 years and 43% of participants were women. A large proportion of the cohort came from poor socio-economic conditions (defined as approximately US$1,500 per annum per household) and only 20% spoke English as their home language. The majority spoke Xhosa, the local African language (48%) or Afrikaans (28%).

The median adherence of the cohort was 93.5% (mean 87.2%). Three times daily dosing [risk ratio (RR), 3.07; 95% confidence interval (CI), 1.40–6.74], speaking English (RR, 0.41; 95% CI, 0.21–0.80) and age (RR, 0.97; 95% CI, 0.94–0.99) were independent predictors of incomplete adherence. Socio-economic status, sex and HIV stage did not predict adherence.

Independent predictors of virologic failure included baseline viral load (RR, 2.57; 95% CI, 1.57–4.22) and three times daily dosing (RR, 2.64; 95% CI, 1.23–5.66), incomplete adherence (RR, 1.92; 95% CI, 1.10–3.57), younger age (RR, 0.96; 95% CI, 0.92–0.99) and dual nucleoside therapy (RR, 2.69; 95% CI, 1.17–6.15).

The investigators also reported that 70.9% of patients on triple therapy maintained a viral load of <400 copies at one year. These adherence and suppression results match or surpass those reported in most observational or clinical trial cohorts in developed countries, where adherence measures indicate that patients take 70% of their antiretroviral medicines and the rate of viral load suppression is 50%.

They also noted that speaking the same language as site staff and simplified dosing regimens were beneficial to good adherence. But, most importantly, they concluded, "…Low socioeconomic status was not a barrier to success. Individuals with HIV disease who could potentially benefit from ART should not be denied access based on otherwise unsubstantiated expectations of poor adherence."

Ref: Orrell C, Bangsberga D, Badri M et al. Adherence is not a barrier to successful antiretroviral therapy in South Africa AIDS 2003, 17:1369–1375

C O M M E N T

Expectation of poor adherence is a major concern in any discussions around scaling up therapy and this study cites the oft quoted UNAIDS spokesman's statement "Ask Africans to take their drugs at a certain time of day and they don't know what you're talking about" which seems to sum up these widely held assumptions.

Yet in contrast to current expectations of non adherence, as with a previous report from Senegal, this group demonstrates that high levels of adherence required to implement successful therapy can be achieved even in the absence of formal adherence interventions.

[Laurent C, Diakhate N, gueye NFN et al. The Sengalese government's highly active antiretroviral therapy initiative:18 months follow up AIDS 2002 16:1363-1370]

ANTIRETROVIRALS

T-20 approved in Europe

On 28 May the European Medicines Evaluation Agency approved T-20 (enfuvirtide, Fuzeon) for use in Europe. T-20 is the first fusion inhibitor to be approved and was developed jointly by Roche and Trimeris.

The indication is for the fairly wordy "use in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected patients who have received treatment with and failed on regimens containing at least one medicinal product from each of the following antiretroviral classes, protease inhibitors, non-nucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors, or who have intolerance to previous antiretroviral regimens. In deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different medicinal products. Where available, resistance testing may be appropriate."

Supply issues may limit initial access to T-20.

Links:

EMEA European Public Assessment Reports

http://www.emea.eu.int/humandocs/Humans/EPAR/fuzeon/fuzeon.htm

Roche press release

http://www.roche.com/med-corp-detail-2003?id=990&media-language=e

Enfuvirtide (T-20): predicting success and modelling survival benefits

http://www.i-base.info/pub/htb/v4/htb4-1/Enfuvirtide.html

C O M M E N T

Results from the T-20 registrational studies (TORO 1 and 2) have been reported in recent issues of HTB [April 2003 and others] and European approval of this new drug is welcomed. While resistance testing is not necessary for T-20 itself, it is critical in choice of background regimen.

As with other new drugs, for optimal benefit, guidelines recommend using at least one-two other drugs to which the patient is sensitive. Use of T-20 as 'virtual monotherapy' with probably limit duration of benefit to 6-12 months, and result in cross-resistance to T-1249, the next fusion inhibitor in the pipeline. In practice, this implies using T-20 earlier in treatment failure, at least by third line.

Other physicians are hoping to delay use of T-20 until availability of new agents such as tipranavir, or other investigational drugs, become available in trials or expanded access. An accurate timeline for access, and adequate supplies once available, are still disappointingly unreliable for new drugs.

Tenofovir European licence extended to include first-line therapy

On 27 May 2003 the European Medicines Evaluation Agency granted approval to expand the indication for tenofovir (Viread) to include the drug's use in treatment-naïve HIV patients in Europe.

The Committee for Proprietary Medicinal Products (CPMP), the scientific committee of the EMEA, issued a positive opinion to expand the indication for tenofovir in February 2003. The Commission's decision is based on 48-week results from Gilead's Study 903 in 600 treatment-naïve patients infected with HIV, including patients with a high viral load (>100,000 copies/mL). [See HTB Jan/Feb 2003]

Tenofovir was first authorised for sale in the European Union in February 2002 for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients experiencing early virological failure.

Source: Gilead Sciences press release

EMEA documents:
http://www.emea.eu.int/humandocs/Humans/EPAR/viread/viread.htm

Gilead press release:
http://www.gilead.com/wt/sec/pr_1053732734

FDA approves atazanavir in US - a once daily protease inhibitor

The Food and Drug Administration (FDA) today announced the approval of atazanavir sulfate (Reyataz), a protease inhibitor to be used in combination with other anti-retroviral agents for the treatment of patients with HIV infection.

Atazanavir is dosed at two pills taken once daily and needs to be taken with food.

Source: FDA press release

Detailed information on atazanavir is available in documents prepared for the FDA hearing in May, one by the FDA, the other by Bristol-Myers Squibb: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3950b1.htm

C O M M E N T

Atazanavir causes fewer cholesterol and triglyceride problems than the other PIs although limited data available has not so far shown that this translates to reduced levels of lipodystrophy.

Atazanavir is likely to require boosting with low dose (100mg) ritonavir in treatment experienced patients, and this doesn't appear to reduce the beneficial lipid profile. Early data also indicates that tenofovir reduces both atazanavir and ritonavir levels by up to 25% and these two drugs should not be used together unless atazanaivr durg levels are confirmed using TDM and dosing individualised.

Atazanavir is currently available in the UK in an expanded access programme and doctors should call Dr Ian Hitchcock on 0208 754 3684 who is respnsible for this programme at BMS.

Atanazavir and saquinavir in salvage therapy: reduced effect on lipids shown in pilot study

Simon Collins HIV i-Base

Atazanavir is the most recently licensed protease inhibitor in the US, and is already available in an expanded access programme in the UK, with full European licensing expected shortly. This pilot dose-ranging atazanavir study shows the potential for atazanavir to boost levels of saquinavir to allow once daily dosing of saquinavir (at 1200mg/day). In addition to reduced dosing, similar efficacy and reduced side effects were obtained compared to the more established twice-daily use of ritonavir/saquinavir (400mg/400mg).

This multinational, randomised 48-week study presented 24-week data at the 41st ICAAC 18 months ago and 48-week results are published in the June issue of AIDS. The study randomised 85 treatment experienced adults from North America, South America and Europe (approx: mean age 39 years, 20% women and 65% white) whose previously undetectable viral load had rebounded >1000 copies/ml. Previous use of ritonavir or saquinavir for >30 days was exclusion criteria, as was use of >2 nucleosides or >1 NNRTI. This was an experienced but not highly experienced group.

Primary endpoints were to assess safety and tolerability of 400mg and 600mg doses of ATZ, each with 1200mg saquinavir plus two physician-selected nucleosides. Secondary endpoints included virological and immunological comparisons of the three arms. Only ATZ dose was blinded and Fortovase formulation of saquinavir was used throughout.

Although fairly well matched, the 400mg ATZ group had statistically a higher proportion of subjects with baseline viral load >30,000 copies/ml

Toxicity management included ensuring that episodes of grade 4 hyperbilirubinemia (bilirubin >5-10xULN) resulted in discontinuation of ATZ until levels of grade 3 or less were reached, and ATZ was then restarted at dose reduced by 200mg. An elevation to >10xULN resulted in permanent discontinuation.

Baseline characteristics and results are shown below:

	ATZ 400mg	ATZ 600mg	RTV/SQV (400/400mg)
n	34	28	23
Prior AIDS diag (%)	11 (32%)	7 (25%)	3 (13%)
Baseline HIV RNA log10 (SE)	4.5 (0.12)	4.28 (0.15)	4.1 (0.4)
Baseline viral load >30,000 c/ml	18 (535) *	10 (36%)	5 (22%)
CD4 cells/mm3 (SE)	346 (30)	319 (32)	330 (30)

** p =0.03 vs RTV arm*

n (received study med)	32	27	23
Mean 24-wk log RNA drop (SE)	-1.28±0.20	-1.11±0.20	-1.50±0.31
Mean 48-wk log RNA drop (SE)	-1.44±0.25	-1.19±0.22	-1.66±0.23

Virological response, defined as either viral load reduction >1log or viral load <400 copies at week 48 (neither of which is particularly associated with durable benefit) was achieved by 41%, 29% and 35% of the ATZ 400mg, ATZ 600mg and RTV groups respectively, and none of the efficacy differences between the arms achieved significance (P=NS).

Discont. before 48 wks (%)	8 (24%)	8 (29%)	12 (52%)
Side effects:	3	3	7
Lost to f/u	1	1	4
Non-Adherence	1	2	1
Other	3	2	-

Lipid profiles improved on the atazanavir arms with total cholesterol, fasting LDL-cholesterol, and fasting triglyceride levels were similar or below baseline levels at 48 weeks. In the ritonavir/saquinavir treatment group clinically significant increases in these parameters were observed of +10%, +23% and +95% respectively.

Ref: Haas DW, Zala C, Schrader S et al - Therapy with atazanavir plus saquinavir in patients failing highly active antiretroviral therapy: a randomized comparative pilot trial. AIDS 2003; 17(9):1339-1349

C O M M E N T

The patient population in this study were those in early treatment failure who had ability to put together a supported salvage regimen. NRTIs were selected based on being </=2.5 times EC50, which may not have been sufficiently sensitive (for d4T and ddI). The lack of adverse effects on lipid profiles clarifies one of the circumstances where this may be a preferred option, but there are concerns about the potency of this combination.

The most stringent comparison for efficacy is likely to be lopinavir/r-based combinations but early results of the BMS-045 study comparing atazanavir+ritonavir, atazanavir+saquinavir and lopinavir/r in more highly treated individuals showed the saquinavir arm to be virologically significantly less effective.

Phase 3 studies of atazanavir used 400mg doses for treatment naïve patients and atazanavir boosted by ritonavir (300/100mg) for treatment experienced patients.

Use of Invirase may produce better absorption, fewer side effects and adherence benefits (smaller capsules, no refrigeration) over Fortovase. The study did not collect or present data on drug absorption, but as with all combinations not formally studied in larger trials that involve drug interactions for which there are little data, confirming adequate drug trough levels using TDM on an individual patient basis is both recommended and readily available in the UK.

This was highlighted by the results from the a sub-study of the French Puzzle-2 trial that showed that drug levels of atazanavir and ritonavir dropped when treatment experienced patients using atazanavir/ritonavir-based regimens added tenofovir to their combination.

Major change to OPTIMA salvage therapy study in the UK

The OPTIMA study has recently received MREC approval for a significant amendment to the trial design. This makes this a more appealing study for both patients and doctors.

Previously, patients were required to enter a two way randomisation both for whether or not to take a treatment interruption prior to changing to a new salvage regimen and for whether to use less than or more than five drugs in their upcoming combination.

The amendment now allows the patient to choose one of these previously randomised factors, and only requires randomisation for the remaining question.

Low recruitment to the original study was partly a result of a lower pool of eligible patients, but also partly because of strong feelings either for or against treatment interruptions or multi-drug therapy.

There is however little reliable evidence for the benefits or risks for these approaches, with small studies indicating conflicting results, even in the short term for a treatment interruption. Similarly, early studies using mega-HAART (with five or more drugs)

are complicated by both sensitivity to drugs and drug exposure and obtaining therapeutic drug levels.

This study now presents a very safe option for patients. Choice of drugs is left to the individual patient and physician, and resistance testing is available to aid this. Additionally, ritonavir, if used as a booster to another PI, is not included within the standard regimen arm (not Mega-HAART), in practice allowing use of five drugs in the reduced drug arm. Therapeutic drug monitoring is already available in the UK for patients on salvage therapy and, as with all decisions for routine clinical care, this is managed by the patient's regular doctor. Similarly, although the study protocol suggests a treatment interruption of 12 weeks, this can be reduced to eight weeks (as suggested by the positive results from the French Giga-HAART study) or extended for a longer period, depending on the individual patient response.

OPTIMA is a tri-national multicentre collaboration between the MRC in the UK, the Veterans Association in the US and the Canadian Trials Network in Canada. The study amendment is only available for patients in the UK.

Links:
http://www.optimatrial.org/

http://www.hivnet.ubc.ca/A167.html

WOMEN

Is stress associated with CIN progression in HIV-positive women?

Polly Clayden, HIV i-Base

A paper published in May/June's *Psychosomatic Medicine* reports findings from a study designed to determine whether "life stress" can be implicated in the progression of cervical intraepithelial neoplasia (CIN).

HIV-positive women are at greater risk from human papillomavirus (HPV) and CIN and they also experience high rates of CIN recurrence and treatment complications. African-American HIV-positive women of low economic status are disproportionately affected by HIV and HPV infections and have high rates of cervical cancer mortality rates. They may be at particularly high risk for CIN progression, recurrence and treatment complications.

Life stress and other psychosocial factors have been implicated in immune decrements in and faster progression to AIDS in both men and women with HIV, and more advanced CIN in HIV-negative women. The purpose of this prospective study was to assess whether life stress was associated with the progression and/or persistence of squamous intraepithelial lesions (SIL), the diagnosis conferred by Papanicolau (PAP) smear in 32 African- and Caribbean- American women coinfected with HIV and HPV after one year follow up.

Inclusion criteria included one abnormal PAP smear in the two years prior to enrolment and CD4 count $\geq$ 150 cells/mm and exclusion included past or current clinical AIDS (category C), a history of high grade SIL or cervical cancer, hysterectomy or treatment for SIL in the year before enrolment.

The women underwent a psychosocial assessment interview, blood draw, coloscopy and HPV cervical swab at study entry. A 10 item abbreviated version of the life experience survey (LES) was used to measure stressful life events.

Using medical chart review, the investigators then abstracted SIL diagnoses at study entry and after a year of follow up. Hierarchical regression analysis revealed that higher life stress increased the odds of developing progressive/persistent SIL over one year by approximately seven-fold after controlling for biological and behavioural covariants (p=0.001).

The authors conclude that these findings suggest that "life stress may constitute an independent risk factor for SIL progression and/or persistence in HIV-infected women. Stress management interventions may decrease risk for SIL progression/ persistence in women living with HIV".

Ref: Pereira DB, Michael AH, Danielson A et al. Life stress and cervical squamous intraepithelial lesions in women with human papillomavirus and human immunodeficiency virus. Psychosomatic Medicine 65:427-434 (2003)

SIDE EFFECTS

FDA says some follow-up drug studies are never started

More than half of the product research that drug companies routinely promise as a condition of sales approval has yet to begin, reports the US Food and Drug Administration. The good news is that companies are fulfilling commitments on drugs given special fast-track approval to treat life-threatening diseases before there's final proof they really work, the FDA said.

Post-marketing research can be crucial for tracking troublesome side effects and, in the case of fast-track drugs, proving a

medicine that alleviates symptoms goes on to lengthen lives.

The FDA has long come under fire for not tracking how much of that promised research actually gets done. The FDA provided a count and a Web site where the public can search how well companies fulfill their commitments. Among the findings:

-Some 60%of 1,339 promised post-marketing studies of drugs have not begun, nor have 30% of 223 promised studies of biological therapies. Some of those studies have stalled for years.

-Many times, FDA didn't set a deadline. Among those that had deadlines, 2% of the drug studies and 8% of the biological studies are classified as delayed.

-Among fast-track drugs, half of the promised post-marketing studies already are completed, 28% have not begun, and 1.6 % are officially delayed.

"It shows there's room for improvement," by companies and FDA, said Dr John Jenkins, director of FDA's Office of New Drugs.

Dr Sidney Wolfe of the consumer advocacy group Public Citizen called the findings grim, saying there are too many unanswered safety questions about big-selling drugs because FDA didn't impose deadlines.

FDA's only recourse if a company balks at a promised study is to pull the drug off the market, which it is reluctant to do. Wolfe wants the FDA to seek congressional authority to impose large fines on companies that stall.

The pharmaceutical industry called the findings "largely good news." The percentage of truly delayed studies "is very small," said Alan Goldhammer of Pharmaceutical Research and Manufacturers of America.

Source: Aetna Intelihealth

FDA statement on the post-marketing study and the full study:
http://www.fda.gov/cber/fdama/pstmrktfdama130.htm

http://www.fda.gov/cder/pmc/

C O M M E N T

PhRMA need to work on their statistics if they think 60%, 30% or 28% of promised post-marketing studies is "very small". Of note, BMS still has 8 ddI (Videx) "ongoing" studies in the FDA "post-marketing commitment" database, although ddI was approved in 1991.

Lamotrigine shows some benefit for HIV-associated painful sensory neuropathies

The objective of this study was to evaluate the efficacy and tolerability of lamotrigine (LTG) for the treatment of pain in HIV-associated sensory neuropathies. In a randomised, double-blind study, patients with HIV-associated distal sensory polyneuropathy (DSP) received LTG or placebo during a seven-week dose escalation phase followed by a four-week maintenance phase. Randomisation was stratified according to whether or not patients were currently using neurotoxic antiretroviral therapy (ART).

The number of patients randomised was 92 (62 LTG, 30 placebo) in the stratum receiving neurotoxic ART and 135 (88 LTG, 47 placebo) in the stratum not receiving neurotoxic ART. Mean change from baseline in Gracely Pain Scale score for average pain was not different between LTG and placebo at the end of the maintenance phase in either stratum, but the slope of the change in Gracely Pain Scale core for average pain reflected greater improvement with LTG than with placebo in the stratum receiving neurotoxic ART ($p = 0.004$), as did the mean change from baseline scores on the Visual Analogue Scale for Pain Intensity and the McGill Pain Assessment Scale and patient and clinician ratings of global impression of change in pain ($p </ = 0.02$). The incidence of adverse events, including rash, was similar between LTG and placebo.

Simpson concluded that lamotrigine was well-tolerated and effective for HIV-associated neuropathic pain in patients receiving neurotoxic antiretroviral therapy. Additional research is warranted to understand the differing response among patients receiving neurotoxic antiretroviral therapy compared with those not receiving neurotoxic antiretroviral therapy.

Ref: Simpson DM, McArthur JC, Olney R, et al. Lamotrigine for HIV-associated painful sensory neuropathies: A placebo-controlled trial. Neurology 2003 May 13;60(9):1508-14

Source: NATAP.org

LIPODYSTROPHY AND METABOLIC COMPLICATIONS

HIV and heart disease: D:A:D prevalence rates show importance of accessing CVD risk in HIV patients

Simon Collins, HIV i-Base

The objective of the EMEA initiated and pharmaceutical sponsored D:A:D study (Data on collection of Adverse events of anti-HIV Drugs) is to describe the prevalence of risk factors for cardiovascular disease (CVD) in HIV-patients and to investigate whether antiretroviral drugs or HIV itself are associated with an increased risk of CVD. Results from both aspects of the study are critical to management of patients using HAART.

This is an ongoing study and the results from data collected to August 2002 were presented at the 10th CROI (Conference on Retroviruses and Opportunistic Infections) in Boston earlier this year and were reported in the March issue of HTB. From almost 36,500 patient-years the study identified 126 cases of myocardial infarction (90% of cases were men, median age 48 years), 25% of which were fatal. In a multivariate analysis these results indicated a cumulative relative risk of myocardial infarction of 1.26 per year of HAART use. [1, 2]

The focus of this article is the results from the analysis of baseline data for the prevalence of risk factors for the cohort, published in 23 May issue of AIDS. [3] This coincided with distribution of a 175-page Supplement from AIDS focusing on HIV-associated CVD in the HAART era. [4] The results have serious implications for management of patient care in the UK, especially coupled with the knowledge that this has translated into increased clinical events.

The D:A:D study is an observational study involving 11 cohorts and includes data from more than 20,000 patients at 188 clinics mainly in Europe but including one cohort each from USA and Australia. These cohorts provide a very broad patient group across diverse national differences. Median age is 39, with 24% women (range: 3% Australia to 31% Italy), 42% homosexually acquired HIV (range: 20% in Italy to 87% in Australia) and 23% IVDU (range: 4% Australia to 40% Spain). Baseline data from this analysis includes almost 18,000 patients from nine of the cohorts.

At enrolment and every eight months thereafter, completed patient forms based on patient interview, case notes and physical exam are completed. In addition to HIV-related health results (CD4, viral load, use of treatment, total cholesterol, HDL cholesterol, triglycerides), this includes age, patient and family history of CVD, smoking status, BMI, blood pressure, diabetes, lipid-lowering and hypertensive therapy and clinical signs of lipodystrophy. Use of ARVs is recorded as naïve, ever-used and current, by RTI only and by PI and NNRTI use.

Results: prevalence of risk factors

At enrolment 13% of study population were ARV-naïve, 6% were previously exposed but not currently on treatment. Eleven percent were on RTI-only, 20% on NNRTI, 43% on PI (>70% ever used) and 7% included all three classes.

Almost 25% were in an age group constituting a study defined risk factor (>45 men, >55 women). Eleven percent had a family history of heart disease (first degree relative with MI when <50 years old) and 1.4% had a previous history of CVD.

Twenty-two percent of subjects had total cholesterol levels >6.2mmol/l which was associated with PI, NNRTI or PI+NNRTI. People who discontinued treatment, whatever their previous treatment history, had similar cholesterol levels to treatment naïve individuals, suggesting reversibility. Risk for elevated cholesterol increased with CD4 count (24% per two-fold increase in CD4).

Triglycerides were elevated in 28% fasted samples and 35% unfasted samples but 40% samples lacked information about fasting status. Risk of cumulative exposure by drug class for elevated triglycerides was 1.05, 1.28, 1.38 in NRTI, NNRTI and PI use respectively (in univariate and multivariate analysis). For people not on treatment only, risk of increased triglycerides correlated with viral load.

Compared to treatment naïve individuals, all regimens were associated with risk of low HDL cholesterol, except those containing an NNRTI, with risk for decreased HDL being highest in patients with low CD4 or high viral load.

Twenty-five percent of patients were recorded as having lipodystrophy, recognisable by physician assessment of either fat loss, fat accumulation or a combination of both and this data was included in 99% of submissions. As expected this was associated with both ARV use and exposure, and also in multivariate analysis with elevated total cholesterol (OR 1.56), elevated triglycerides (OR 2.16) and decreased HDL (OR 1.56).

Although more than 8% of the study population had hypertension, this correlated with age, sex and BMI and not antiretroviral use, but it highlights the importance of considering hypertension as an additional health concern for cohorts of HIV-positive patients. However, lipodystrophy and diabetes were both associated with hypertension (OR 1.34 and 2.05 respectively). Overall prevalence of diabetes was 2.5%.

Taken together these results highlight the growing range of health concerns that will impact on the health of HIV-positive patients and their primary providers of healthcare (which are increasingly their HIV-treating physicians).

While there are limitations from the observational design and cross sectional nature of this analysis – these results present associations and do not show causality – this is still by far the largest study of its kind to prospectively look at both events and the wide range of contributory risk factors.

In the discussion the authors refer to the limitations from data collection and incidence on missing data current smoker (18%), family history (37%), total cholesterol (18%), HDL cholesterol (54%) and triglyceride (18%). Although there was an uneven distribution of missing data from cohorts this was accounted for in the analysis. Information on other important risk factors such as diet, exercise, alcohol and genetic factors were not included, but by their nature would also be unlikely to standardise with such large patient numbers and international differences.

It is impressive that this study was initiated at a European level as a safety issue, and that it has been funded collectively by all the major manufacturers of antiretroviral drugs. It is also very reassuring that these companies have committed continued funds to extend the data collection for at least a further two years.

Full text from the AIDS article is available at:
http://www.natap.org/2003/may/052803_3.htm

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C O M M E N T

One of the controversial aspects of the results is that these findings are in contrast to a retrospective analysis of the US Veterans Association database of over 36,000 patients, which was presented at Retrovirus Conference in 2002 and which had found no increase in reports of cardiovascular events between pre-HAART years and in the years that HAART has been widely available (January 1993-June 2001).

Presentation of the D:A:D study at Retrovirus this year overlapped with the publication of the VA study with commentary in 20 February edition of the NEJM. [5, 6]

Neither D:A:D nor VA database studies are perfect but the increased risk shown in the European study is already reflected in treatment guidelines that include making an assessment of risk factors for CVD prior to starting patients on antiretroviral therapy.

HAART increases body fat at first; both d4T and AZT lead to subsequent fat loss

Simon Collins, HIV i-Base

Evaluation of the contribution of individual drugs and HAART itself to the varied manifestations of the lipodystrophy syndrome was hampered in early studies by poor monitoring, limited duration and subjective and retrospective reporting. In addition to linking peripheral fat loss to both d4T and AZT-containing regimens and highlighting an increase in fat over the initial months of treatment that is not generally appreciated by patients concerned about the risk of lipodystrophy, important observations on blood lipids and bone mineral density were also reported in this Australian study.

This prospective study, published in 2 May issue of AIDS, recruited 40 treatment naïve men (median age 39, IQR 30-49) between July 1997 and May 2000, monitoring them at baseline, and 12 and 24 weeks after starting treatment and every 24 weeks thereafter. Median CD4 and viral load were 246 cells/mm3 (IQR 62-430 cells/mm3) and 5 log copies/ml (IQR 4.3-5.7 copies/ml).

The primary hypothesis was that lipoatrophy occurs as a result of HIV therapy, with primary endpoint change of limb fat measured by DEXA. Secondary endpoint included change in abdominal fat and other metabolic parameters. Choice of

treatment was non-randomised and left to the individual doctor and patient. In addition to the routine parameters of CD4, viral load, fasting total cholesterol (TC), LDL and HDL cholesterol, triglycerides (TG), glucose and insulin, DEXA scans from a single site were used to assess changes in central abdominal fat (CAF), limb fat (LF) and lean mass (LM), and spinal bone mineral density.

At the time of analysis 90% and 50% of patients had been followed for 96 and 144 weeks respectively. All median baseline parameters were within normal limits. Almost half the group started treatment with a PI, five using PI+NNRTI-based treatment. Dual nucleoside background was equally distributed between ddI+d4T, d4T+3TC or AZT+3TC.

40% of men changed treatment over the course of the study, nearly all related to toxicity management, none related to lipodystrophy. Most changes did not occur during the first months of treatment although 11 changes from d4T occurred after a mean of seven months (three-12 months).

The following key results relating to body changes were reported:

- BMI increased significantly (22.5 to 24, P<0.05) and lean mass increased by 3% (p<0.01) by week 12, which was sustained to week 48, and returned to baseline by week 96.
- Total body fat increased by median 20% by week 24 (p<0.001) but was significantly higher in PI vs NNRTI-based therapy, and remained stable thereafter.
- Limb fat (5.6 vs 6.9kg) central fat (1.0 vs 1.3kg) and lean mass (52.5 vs 54.7kg) all increased over first 24 weeks (coinciding with greatest viral load and CD4 changes).
- From week 24 there was a selective and progressive loss of limb fat [median 13% (QR 0.9-26.3) loss per year] with d4T most significantly associated with increased rate of loss in multivariate analysis.
- Central abdominal fat was significantly higher in patients using PI- compared to NNRTI-based combinations. Increases in CAF at week 24 were maintained after week 24 and remained significantly higher than baseline at week 144.
- Hypercholesterolaemia developed early in treatment, whereas hypertriglyceridaemia, hyperinsulinaemia and decreased bone mineral density developed later.
- Bone mineral density T-score rose slightly to week 24 and fell significantly to week 48, maintained over follow up. Percentage of people with osteopenia (T-score <1.0) increased from 13% at baseline to 22% at week 144, although only one additional score consistent with osteoporosis (T-score < - 2.5) was noted during the study.
- The largest changes in CD4 cell counts and HIV viral load, seen early into treatment, were associated with gain rather than loss of fat.

The authors conclude that this is the first prospective study demonstrating that treatment with antiretrovirals results in progressive, selective loss of limb fat. Also that the loss of limb fat occurred after the period of most intense immune restoration, making an immune aetiology unlikely.

Ref: Mallon PWG, Miller J, Cooper DA, Carr A - Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy. AIDS 2003; 17(7):971-979

C O M M E N T

Because the study first started recruiting in 1997 only shortly after combination therapy became widely available, it is likely to include a number of patients with more advanced HIV disease. This may explain some of the early increases in weight and lean mass – but similar results have been reported in a recent ACTG study.

However the link of both d4T and AZT treatment to lipoatrophy is very important, and with availability of a wide range of nucleosides for initial therapy, many doctors are choosing not to use either drug in first line therapy. This has been reflected in the recent decision not to recommend d4T for initial therapy in the BHIVA guidelines.

The report of bone mineral changes over such a short period again highlights the potential role for baseline DEXA scan prior to treatment.

Lipoatrophy improved by switching from d4T to abacavir

Graham McKerrow, HIV i-Base

Abacavir (ABC, Ziagen) represents a virologically effective replacement for d4T, PI, or NNRTI in people on successful first-line therapy, concludes a British study. The authors report that replacement of a PI or NNRTI with ABC leads to modest improvement in both cholesterol and triglycerides. Replacement of d4T with ABC leads to modest improvements in fat mass.

This was an open-label randomised study of HIV-positive individuals on a first-line therapy containing stavudine (d4T) with either a protease inhibitor (PI) or nonnucleoside reverse transcriptase inhibitor (NNRTI) and with hypercholesterolemia (defined as total cholesterol >5.2 mmol/L or >180 mg/dL) and/or lipoatrophy and with a viral load of <50 copies/mL. Patients switched d4T to abacavir (ABC) (group 1), a PI or NNRTI to ABC (group 2), or d4T and PI or NNRTI to ABC plus AZT (group 3). Patients were followed-up with fasting blood levels, dual-energy X-ray absorptiometry (DXA), and computed tomography (CT) scans for 48 weeks.

Patients were eligible for inclusion if they (1) were HIV-positive and on a first-line therapy containing d4T with either a PI or an NNRTI, (2) had hypercholesterolemia (defined as total cholesterol >5.2 mmol/L or >180 mg/dL) and/or clinical lipoatrophy, and (3) had a viral load <50 copies/mL. Lipoatrophy was assessed as described in the entry criteria for the HIV lipodystrophy case definition study, involving patient- and physician-agreed moderate or severe lipoatrophy at one or more sites.

Thirty patients were included, with 27 completing 48 weeks of therapy. One ABC hypersensitivity reaction was the only serious adverse event. All patients' viral loads remained at <50 copies/mL. CD4 cell counts rose in groups 2 and 3 but fell modestly in group 1. Total and low-density lipoprotein cholesterol improved significantly in groups 2 and 3. Triglycerides fell significantly in group 2. In contrast, total, arm, and leg fat mass (by DXA) rose significantly in group 1 but fell modestly in groups 2 and 3. Visceral adiposity (by CT scan) was unaffected in all groups.

The study evaluated three possible approaches to manage lipid, insulin, and morphologic changes in persons on d4T plus PI-based or NNRTI-based first-line antiretroviral regimens. With all approaches, ABC maintained virologic control and significant differences in CD4 cell count were not observed. Previous studies using ABC or ABC plus AZT-based substitutions have indicated that virologic control is maintained in first-line therapy patients but less reliably in individuals with prior incomplete viral suppression of thymidine-based therapy or known archived nucleoside analogue resistance mutations. Pretreatment CD4 count and viral load do not appear to affect the efficacy of ABC-based regimens when ABC is used as a substitution agent in individuals with full viral suppression on first-line therapy.

For the management of hypercholesterolemia, total and LDL cholesterol improved significantly when the PI or NNRTI was replaced by ABC. In their Discussion, the authors write that these data are consistent with several previous reports of this substitution approach. Data from a randomised study comparing PI replacement with ABC, nevirapine, or efavirenz found declines in total cholesterol to be greatest in the group switched to ABC. These data suggest that replacement of d4T with ABC in these circumstances may lead to modest rises in total cholesterol. As with this study, a similar nonsignificant rise in total cholesterol was observed in a larger 24-week randomised study of this approach. These small rises in cholesterol and triglycerides are not of sufficient magnitude to influence cardiovascular risk meaningfully, write the authors.

None of the substitution approaches led to significant improvements in HDL cholesterol, triglycerides, insulin, or lactate over 48 weeks, although groups 2 and 3, which involved the replacement of a PI or NNRTI with ABC, indicated trends to improvement in triglycerides and insulin consistent with larger studies.

Fat mass in both arms and legs improved significantly over 48 weeks when d4T was replaced by ABC. However, this benefit was not observed when the d4T-based regimen was replaced with one containing AZT.

The authors add: "Most intriguingly, lipids and insulin levels rose in the group where fat mass recovered but fell in the populations where fat mass did not recover. This suggests that these factors are incompletely (at best) linked."

They conclude: "In summary, replacement of d4T, PI, or NNRTI in first-line therapy patients with ABC maintains virologic control. Replacing d4T with ABC leads to improvements in limb fat mass, but these improvements are not accompanied by improvements in fasting lipids. Replacement of a PI or NNRTI with ABC is associated with improved fasting cholesterol (with trends to better triglycerides and insulin levels) but without benefits to fat mass."

Ref: Moyle GJ, Baldwin C, Langroudi B et al. A 48-week, randomised, open-label comparison of three abacavir-based substitution approaches in the management of dyslipidemia and peripheral lipoatrophy. Journal of Acquired Immune Deficiency Syndromes May 1, 2003; 33(1):22-28.

This paper can be found at:
http://www.natap.org/2003/may/052803_4.htm

IMMUNOLOGY

T cell activation is associated with decreased CD4+ T cell gains during ARV therapy

Graham McKerrow, HIV i-Base

Persistent T cell activation is associated with decreased CD4+ T cell gains during therapy, according to researchers in San Francisco. They found that increased T cell activation was associated with shorter duration of viral suppression, hepatitis C coinfection, frequent low-level viremia, and lower nadir CD4+ T cell counts.

Although T cell activation is associated with disease progression in untreated human immunodeficiency virus type 1 (HIV-1) infection, its significance in antiretroviral-treated patients is unknown. For this study activated (CD38+HLA-DR+) T cell counts were measured in 99 HIV-infected adults who had maintained a plasma HIV RNA level 1000 copies/mL for a median of 21 months while receiving antiretroviral therapy. Patients with sustained viral suppression had lower levels of T cell activation than untreated patients but higher levels than HIV-uninfected control subjects. Persistent T cell activation was associated with decreased CD4+ T cell gains during therapy. For every 5% increase in the proportion of activated CD8+ T cells, 35 fewer CD4+ T cells/mm3 were gained. Increased T cell activation was associated with shorter duration of viral suppression, hepatitis C coinfection, frequent low-level viremia, and lower nadir CD4+ T cell counts. Interventions that directly target T cell activation or the determinants of activation may prove to be useful adjuvants to antiretroviral therapy, say the authors.

Participants were selected from the Study of the Consequences of the Protease Inhibitor Era (SCOPE), a clinic-based cohort of 450 chronically HIV-infected patients who receive primary care in HIV/AIDS clinics. The cohort was assembled to represent distinct groups of HIV-infected persons: 25% of participants were untreated at enrollment; 50% were receiving HAART but were in a state of virologic failure at enrollment, with plasma HIV RNA levels consistently >1000 copies/mL for at least 24 weeks; and 25% were receiving HAART at enrollment and had been experiencing virologic suppression with plasma HIV RNA levels consistently <50 copies/mL for at least 24 weeks, with allowance for occasional transient detectable viremia 1000 copies/mL. Participants were seen at four-month intervals, at which times a detailed questionnaire that collected information about antiretroviral use and risk behaviour was administered and blood and saliva specimens were obtained. The first 175 consecutive SCOPE participants had immunophenotyping of T cells performed at the second study visit. Participants were included in the present analysis if they were receiving HAART, had a plasma HIV RNA level 1000 copies/mL on the day of immunophenotyping and for at least three months before immunophenotyping, and had a documented CD4+ T cell count determination within six months before the initiation of HAART.

Among HIV-infected participants with a median of almost two years of HAART-mediated viral suppression, the researchers found substantial levels of both CD4+ and CD8+ T cell activation, well above the levels observed in HIV-uninfected persons. Furthermore, higher levels of CD4+ T cell activation were independently associated with lower CD4+ T cell gains experienced in the first three months of therapy, and higher levels of CD8+ T cell activation were independently associated with lower CD4+ T cell gains after month three. These results provide further support for the hypothesis that T cell activation plays a critical role in HIV pathogenesis, the authors write.

Their finding that increased CD8+ T cell activation was associated with lower CD4+ T cell gains after three months of HAART-mediated viral suppression is consistent with other work relating CD8+ T cell activation to disease progression in untreated patients.

They write that it is also interesting that HIV-infected patients maintaining viral suppression in this study had substantially higher levels of T cell activation than did HIV-uninfected control subjects. This difference was observed even when HIV-infected participants with persistent detectable viremia or hepatitis C virus coinfection were excluded.

In their discussion, the authors write: “Because the half-life of activated CD4+ and CD8+ T cells is short, the presence of heightened T cell activation after years of suppressive HAART suggests the presence of ongoing antigenic stimulation. This might reflect ongoing low-level HIV replication in lymphoid tissues; the presence of other chronic infections, as a result of continued immunodeficiency (eg herpesvirus infections); or persistent immunologic dysregulation that is not reversed by HAART-mediated viral suppression.

“Although abnormal levels of T cell activation were observed in our participants, it is notable that the levels appeared to decrease as the duration of viral suppression increased. We did not perform repeated measurements over time and therefore cannot exclude the possibility that patients with high levels of persistent T cell activation were preferentially excluded from our sample because of virologic failure; however, the observed association was not confounded by the extent of low-level viremia and suggests that levels of CD8+ T cell activation continue to decrease for years after viral suppression is achieved. This might reflect a continued, albeit gradual, decrease in the level of viral replication that remains below the level of detection of standard plasma HIV RNA assays and/or it might reflect the slow decay of the latent reservoir of infected cells. In either case, a slow decrease of CD8+ T cell activation over time might be one explanation for the slow, but persistent, CD4+ T cell gains observed in the majority of patients with long-term HAART-mediated viral suppression.

“Our finding that persistent CD4+, but not CD8+, T cell activation during suppressive HAART is associated with decreased CD4+ T cell gains in the first three months of therapy suggests that redistribution of CD4+ T cells from lymphoid tissue is more closely associated with a decrease in CD4+ T cell activation than with a decrease in CD8+ T cell activation. Because most patients with untreated HIV infection have high levels of pre-HAART CD4+ T cell activation], we can assume that those patients with the lowest levels of CD4+ T cell activation during suppressive HAART were likely to have had the largest decrease in T cell activation in the first few months of therapy. Because CD4+ T cell activation is closely associated with cell adhesion molecule and chemokine receptor expression, we can speculate that a large reduction in CD4+ T cell activation is associated with a large redistribution of CD4+ T cells from lymphoid tissue.

“In summary, we have shown that abnormal levels of T cell activation exist in most patients experiencing long-term HAART-mediated viral suppression and that the extent of activation is associated with treatment-associated CD4+ T cell gains.

Improving our understanding of how HIV activates the immune system may lead to the development of more-specific adjuvants to HAART that reverse the immunologic perturbations caused by HIV infection."

Ref: Hunt PW, Martin JN, Sinclair E et al. T Cell Activation Is Associated with Lower CD4+ T Cell Gains in Human Immunodeficiency Virus-Infected Patients with Sustained Viral Suppression during Antiretroviral Therapy. J Infect Dis. 2003 May 15;187(10):1534-43. Epub 2003 Apr 23.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12721933&dopt=Abstract

Structured treatment interruptions trial shows no benefit

HIVandHepatitis.com

According to the "autovaccination hypothesis," re-exposure to HIV during treatment interruptions may stimulate the HIV-specific immune response and lead to low viremia after withdrawal of highly active antiretroviral treatment (HAART).

Many patients who started HAART earlier in their disease course than is currently recommended would like to discontinue, but it is unknown whether it is safe to do so.

The objectives of this study were to determine whether repeated treatment interruptions of HAART (1) stimulated the cytotoxic HIV-specific immune response and whether such stimulation correlated with low viremia off treatment, and (2) were safe with respect to clinical complications, development of viral resistance, and decline in CD4 cell counts.

A total of 133 patients at outpatient clinics of university hospitals in Switzerland and Spain received HAART. Participants had a median CD4 cell count of 740/microlitre, and undetectable viral load for a median of 21 months.

HAART was interrupted for two weeks, restarted, and continued for eight weeks. After four such cycles, treatment was indefinitely suspended 40 weeks after study entry.

HIV-specific cytotoxic T-cell responses were evaluated by interferon enzyme-linked immunospot analysis. The proportion of "responders" (viral load <5000 copies/mL) was measured at weeks 52 and 96. HIV-related diseases and CD4 cell counts were recorded.

Seventeen percent of patients (95% confidence interval, 11%-25%) were responders at week 52, and 8% at week 96. Low pre-HAART viral load and lack of rebound during weeks 0 to 40 predicted response. HIV-specific CD8+ T cells increased, but there was an inverse correlation between response and the number of spot-forming cells.

Eighty-five (64%) of 133 patients stopped therapy for at least 12 weeks, and 55 (41%) for at least 56 weeks. The median CD4 cell count decreased from 792/microlitre to 615/microlitre during the first 12 weeks without treatment, but stabilised thereafter. One patient (0.75%) developed drug resistance necessitating salvage treatment. There were no AIDS-related clinical complications.

The authors conclude, "Results of this study do not favour the autovaccination hypothesis. Treatment interruptions did not provoke clinical complications, and there was little drug resistance. Comparative trials will have to show what benefit, if any, is associated with intermittent, as opposed to continuous treatment."

Ref: Catherine Fagard et al (for the Swiss HIV Cohort Study). A prospective trial of structured treatment interruptions in human immunodeficiency virus infection. Archives of Internal Medicine 2003;163:1220-1226.

Source: HIV&Hepatitis.com
http://www.hivandhepatitis.com/recent/sti/053003a.html

OPPORTUNISTIC INFECTIONS

New antibiotic appears effective against MDR-TB

A new antibiotic appears effective against strains of tuberculosis resistant to nearly all currently available treatments. The antibiotic, linezolid (Zyvox), recently saved the lives of four women and one girl who were gravely ill with multidrug-resistant tuberculosis at New York City's Bellevue Hospital, according to a report by physicians from New York University School of Medicine. The patients, aged 10 to 54, were resistant to at least eight, and up to 14, TB therapies.

"They were in a lot of trouble, and we had run out of treatment options," said William Rom MD, professor of medicine and

environmental medicine at NYU School of Medicine. “Trying the linezolid was a real act of desperation,” said Timothy Harkin MD, assistant professor of medicine and assistant director of Bellevue’s chest service. “This certainly seems like a promising medication for multidrug-resistant TB and there is a continuing need for new antibiotics for this disease,” he said.

Harkin and Rom said further studies were needed to confirm their case reports, and they hoped the drug will be tested in large clinical trials sponsored by the World Health Organisation. The NYU physicians presented the cases to colleagues at the 99th International Conference of the American Thoracic Society in Seattle.

Linezolid is a new class of antibiotic that was approved by the US Food and Drug Administration to treat certain strains of bacteria resistant to standard penicillin and methicillin and to more powerful drugs like vancomycin. It is not approved to treat drug-resistant TB. However, Bellevue doctors decided to try linezolid when all other available therapies, including the most powerful drugs yet available for drug-resistant TB, failed to improve the health of the five patients.

Patients took linezolid twice a day in pill form for 9-33 months. Four patients also received interferon gamma in an aerosolised form three times a week. Following treatment, there was no sign of TB in sputum from the patients’ lungs. Moreover, physicians said that the drug did not seem to be associated with many severe side effects. Two patients continue on treatment and are doing well. One patient relapsed two years after completing treatment, but died of unrelated causes before she could be retreated.

Ref: W Rom, T Harkin. Linezolid: A promising new agent for multi-drug resistant tuberculosis treatment. 99th International Conference of the American Thoracic Society in Seattle, Abstract P621. Presented 21 May 2003

Source: CDC Daily Summaries

C O M M E N T

Multi-drug resistant TB (MDR-TB) is tuberculosis resistant to isoniazid and rifampicin - the two most effective first-line anti-TB drugs – and often to additional other drugs. There are, however, at least three other first-line agents, and nine second-line agents licensed against tuberculosis, but MDR-TB remains a difficult disease to treat and is associated with high morbidity and mortality.

This early report suggests that linezolid, an oxizoladone, effective against methicillin-resistant Staphlococcus aureus (MRSA), may have *in vivo* activity against MDR-TB. The *in vitro* anti-TB activity of oxazolidones has been under investigation since the 1980s.

In this report, all five patients achieved sputum culture conversion in a mean of 40 days. However, linezolid is not without side-effects. One of the major concerns with this drug has been myelosuppression (an FDA warning was issued in March 2001), and even in this small series one patient developed neutropenia requiring temporary drug discontinuation. Linezolid cost around a $100 a day, and although further clinical studies are warranted, it may not be the ideal anti-TB drug in resource-poor settings, where the threat from MDR-TB is the greatest.

Tobacco use increases risk for pulmonary diseases and weakens response to therapy in patients on HAART

HIVandHeptatis.com

The increased risk of developing lung diseases in cigarette smokers has been well recognised. The association between smoking and the risk of developing pulmonary infections in HIV-1-infected patients, however, has not been established.

Researchers from the Department of Psychiatry and Behavioral Sciences at the University of Miami evaluated the effect of tobacco use on respiratory infections in HIV positive patients on HAART. Twenty-seven cases with lower respiratory infections (15 cases of PCP, 12 cases of TB) were compared with the same number of age, gender, socio-economic and HIV status-matched patients, without history of respiratory diseases. Medical history and physical examinations were obtained every six months. Blood was drawn for CD4 and viral load measurements.

A substantial number of HIV-positive smokers who developed PCP (one-third) had been on highly active retroviral therapy (HAART) for more than six months and prophylaxis had been discontinued.

Multivariate analyses indicated that in HIV-infected people, after controlling for HIV status and antiretrovirals, cigarette smoking doubled the risk for developing PCP ($p = 0.01$). Multivariate analyses demonstrated that long-term smoking also increased the risk (2 x) of developing tuberculosis ($p = 0.04$).

Moreover, daily tobacco use seemed to attenuate by 40% the immune and virological response to antiretroviral therapies.

These findings indicate that tobacco use significantly increases the risk of pulmonary diseases in HIV-infected subjects and has a potential deleterious impact on antiretroviral treatment.

Ref: MJ Miguez et al. MJ Impact of tobacco use on the development of opportunistic respiratory infections in HIV seropositive patients on antiretroviral therapy. Addict Biol 8(1): 39-43. March 2003.

Source: HIVandHepatits.com
http://www.hivandhepatitis.com/recent/ois/051903f.html

EBV levels in HIV-positive patients are not reduced by HAART

HIVandHeptatis.com

The proportion of HIV-infected patients with high levels of Epstein-Barr virus (EBV) is not affected by highly active antiretroviral therapy (HAART), Dutch investigators report. Thus, clinicians should still test patients for EBV despite the recent decrease in EBV-lymphoma-related morbidity.

In 1999, a research team led by Dr Servi JC Stevens, of the Vrije University Hospital in Amsterdam collected whole blood and parallel plasma samples from 109 patients being treated with HAART. Although all patients had an asymptomatic EBV infection, none developed AIDS-related non-Hodgkin's lymphoma during follow-up until November of 2001.

The investigators report in the 3 May issue of AIDS that 64 whole-blood samples were polymerase chain reaction (PCR) positive for EBV, and 22 of these had 2,000 or more copies of EBV DNA per mL of blood. However, no cell-free virus was detected in plasma samples. There was no correlation between EBV DNA levels and HIV RNA levels or CD4 counts.

Compared with samples collected between 1993 and 1996 from 99 patients receiving anti-HIV monotherapy, no significant difference in EBV DNA loads was observed. Thus, the authors infer, HAART does not affect EBV burden.

The EBV DNA loads in some HIV-infected individuals "are remarkably higher than those found previously in healthy EBV-seropositive donors, who invariably have <2,000 EBV DNA copies/mL blood," the investigators note. They suggest that this indicates a partially impaired immune surveillance against EBV in the presence of HIV.

Dr Stevens' team noted a disparity in IgG responses to EBV VCA-p18 protein and the EBNA-1 protein. In the 14 patients with the highest EBV DNA loads, the anti-VCA-p19 IgG responses were significantly higher than those of patients with undetectable EBV DNA loads ($p < 0.0001$). However, anti-EBNA-1 IgG responses were significantly lower ($p = 0.005$). This observation indicates "impaired latency control and increased lytic replication," the authors write.

Dr Stevens and colleagues suggest that monitoring EBV DNA load and EBV serology may help identify patients at increased risk for lymphomagenesis.

Ref: Stevens SJ, Blank BS, Smits PH et al. High Epstein-Barr virus (EBV) DNA loads in HIV-infected patients: correlation with antiretroviral therapy and quantitative EBV serology. AIDS. 2002 May 3;16(7):993-1001.

Source: HIVandHepatitis.com
http://www.hivandhepatitis.com/recent/malignancies/053003h.html

The efficacy of fluconazole (Diflucan) 600 mg/day versus itraconazole (Sporanox) 600 mg/day for treatment of cryptococcal meningitis in AIDS patients

Cryptococcal meningitis, a life-threatening infection caused by cryptococcus neoformans, is one of the major opportunistic infections that affect people with AIDS. The results of treatment, when following current dosing recommendations, are still unsatisfactory, according to the authors of this report.

The objective of the current study was to evaluate higher than recommended doses of oral fluconazole (Diflucan) and itraconazole (Sporanox) as primary therapy for cryptococcal meningitis in AIDS patients.

HIV positive patients with primary cryptococcal meningitis, who had been treated initially with amphotericin B for two weeks were included in this study. They were randomised into two groups: (1) to receive either fluconazole 600 mg daily or (2) to receive itraconazole 600 mg daily for 10 weeks. The response to the two different regimens was defined as successful if after 10 weeks of treatment no clinical symptoms and signs of meningitis remained and the cerebrospinal fluid (CSF) fungal culture was negative.

The trial was performed from April 1999 to April 2000 at Srinagarind Hospital, Khon Kaen, Thailand. Of the 35 patients who proved for the final evaluation of the study, 19 cases were assigned to the fluconazole regimen and 16 to the itraconazole group.

Ten weeks after treatment, all patients recovered completely. The CSF sterilisation rate for the fluconazole group and for the itraconazole group were 100% and 94%, respectively.

The results of this study indicate that treatment with either 600 mg/day of fluconazole or itraconazole as primary treatment have the same efficacy for AIDS patients with cryptococcal meningitis.

According to the study authors: “The results of this study also suggest that treatment with the higher doses (600mg/day vs 200mg/day) may be superior to treatment regimens using lower doses, as can be judged from the clinical outcome and the results of the mycological cultures.”

Source: HIVandHepatitis.com
http://www.hivandhepatitis.com/recent/ois/052803f.html

Ref: P Mootsikapun et al. The efficacy of fluconazole 600 mg/day versus itraconazole 600 mg/day as consolidation therapy of cryptococcal meningitis in AIDS patients. Journal of the Medical Association Thailand 86(4): 293-298. April 2003.

C O M M E N T

The landmark study that has defined the current standard of care for cryptococcal meningitis was published by the ACTG and the Mycoses Study group in 1997 (van der Horst C et al. NEJM 1997; 337: 15-21). This established the efficacy of induction therapy with intravenous amphotericin B and flucytosine followed by ten weeks of oral fluconazole (400 mg/day). In that study fluconazole maintenance therapy was superior to itraconazole (400 mg/day) in terms of CSF sterilisation (72% vs. 60%, p=0.05).

This study uses higher doses of maintanence oral fluconazole and itraconazole (600 mg/day), and although the numbers are small, suggests equivalent rates of CSF sterilisation. Itraconazole has poor CSF penetration and an unpredictable oral bioavailability, and careful attention to potential toxicity, drug interactions and serum levels are required. Intravenous induction therapy with amphotericin and flucytosine for the first two weeks is still required.

However, voriconazole, a new azole anti-fingal agent with proven efficacy against invasive aspergilliosis (as compared to amphotericin), has activity against *cryptococcal* species and good CNS penetration and may be the oral agent of choice in the future.

PAEDIATRICS

Risk factors for paediatric HIV malignancies

Polly Clayden, HIV i-Base

A paper published in *JAMA* reported findings from a study designed to identify risk factors for malignancy among HIV-positive children.

This multicentre case-controlled study evaluated 43 children with a new malignancy and 74 children without a malignancy based on the duration of their HIV infection. The children were enrolled between January 1992 and July 1998.

Possible risk factors assessed included: demographic characteristics, HIV characteristics, previous antiretroviral treatment and CD4 cell count. Coviral infections with Epstein-Barr virus (EBV), cytomegalovirus (CMV) and human herpes virus 6 were assessed by semiquantative polymerase chain reaction (PCR) assays and serological testing.

Malignancy diagnoses included 28 cases of non-Hodgkin lymphoma, four B-cell acute lymphoblasic leukemia, one Hodgkin disease, eight leiomyosarcoma, one hepatoblastoma and one schwannoma.

The investigators reported that for children with CD4 counts of ≥200 cells /mm3, EBV viral load of greater than 50 viral genome copies per 10^5 peripheral blood mononuclear cells (PBMC) was strongly associated with cancer risk ($p<0.001$) but there was no association for children with CD4 counts of <200 cells ($p=0.99$). They also found that ZDV antiretroviral therapy offered no significant protective effect against malignancies for either the high or low CD4 groups. Additionally route of HIV infection was not associated with increased cancer risk.

They added: “The pathogenesis of HIV-related paediatric malignancies remains unclear and other contributing risk factors can be elucidated only through further study.”

Ref: Pollock BH, Jensen HB, Leach CT et al. Risk factors for paediatric human immunodeficiency virus-related malignancy. JAMA. 289:2393-2399.2003

C O M M E N T

Malignancies in children have always been a relatively rare complication of HIV infection. They accounted for less than 2% of AIDS-defining illnesses in the early natural history studies, presumably because children were dying of other complications before malignancies manifested themselves.

Clearly this cohort was mostly enrolled pre-HAART. We are seeing very few new malignancies in children on HAART, but need to remain vigilant, as they do still occur. In addition, in children of families from sub-Saharan Africa, the incidence of Kaposi's sarcoma is increasing.

TREC analysis shows little thymic damage in HIV-positive adolescents

Polly Clayden, HIV i-Base

A report published in the March issue of Clinical and Diagnostic Laboratory Immunology examined TREC values in a cohort of HIV positive adolescents.

T-cell receptor rearrangement circles (TREC) are DNA molecules that arise during T-cell development, and are present in cells that have recently emigrated from the thymus. During T-cell differentiation in the thymus gland, progenitor cells undergo T-cell receptor rearrangements. These result in the production of episomal DNA by-products called T-cell receptor rearrangement excision circles (TREC). Because TREC do not replicate with mitosis, they are diluted by cell division or lost with cell death. Recently developed tests allow TREC to be quantitated in peripheral blood mononuclear cells and in circulating CD4 cells specifically, as an estimate of thymic output.

The authors explain that "In cross sectional studies, the number of peripheral blood lymphocytes bearing TREC decreases with age, consistent with an anatomically demonstrated loss of thymic epithelial tissue. TREC numbers increase following haematopoietic stem cell transplantation and during therapy for human immunodeficiency virus (HIV) infection." Therefore quantitation of TREC has been proposed as a parameter of thymic activity.

The investigators used real time polymerase chain reaction (PCR) to quantify TREC in blood samples from HIV-negative adolescents and found TREC values in blood T-cells very stable throughout adolescence ,which they explained was once believed to be a time of rapid involution of the thymus.

In addition, in cross sectional analysis they evaluated TREC values in a cohort of HIV-positive vertically infected adolescents and found evidence of ongoing thymopoiesis despite lifelong infection. The investigators conclude: "These data demonstrate the utility of TREC assessment in adolescents and that HIV infection does not uniformly result in accelerated thymic involution in childhood."

Ref: Pham T, Belzer M, Church JA et al. Assessment of thymic activity in human immunodeficiency virus-negative and positive adolescents by real-time PCR quantitation of T-cell receptor rearrangement excision circles. Clin Diagn Lab Immunol 10(2): 323-8;March 2003

C O M M E N T

The reality is that TREC assessment is a useful research technique which provides optimistic evidence for continued immune reconstitution throughout childhood in response to HAART. TREC assays are not useful for clinical monitoring of individual children.

It would be interesting to know when TREC begin to decline to adult levels if they are stable throughout adolescence. Hopefully the investigators will continue to follow the HIV-uninfected adolescents they recruited.

Metabolic abnormalities in protease inhibitor-treated and protease naïve children

Polly Clayden, HIV i-Base

There is currently a paucity of data pertaining to what is broadly termed the lipodystrophy syndrome, in children. A report published in AIDS compares the glucose homeostasis and serum lipid profiles of PI-treated and PI-naïve HIV-positive children and the abdominal adiposal tissue distribution of PI–treated, PI –naïve and HIV-negative children.

This was a cross-sectional study involving HIV-positive children (30 PI-treated, 20 PI-naïve), three–18 years of age, 76% prepubertal, in a paediatric tertiary care centre. PI treated was defined as treatment for a minimum of three months prior to enrolment. The mean duration of PI therapy in the PI group was 22 –/+8.9 months. PI treated was defined as receiving HAART plus at least two non-PI drugs. The children were receiving ritonavir (n=12), nelfinavir (n=13), indinavir (n=2), lopinavir (n=1),

ritonavir+nelfinavir (n=1), and nelfinavir+saquinavir (n=1). In the PI-naive group four were antiretroviral naïve, 14 were on two NRTI and two were on two NRTI and an NNRTI. A group of 52 uninfected underwent CT scan as an additional comparison with respect to abdominal tissue distribution.

Total, HDL and LDL-cholesterol, triglycerides, glucose, insulin, proinsulin and C-peptide were determined in the fasting state. Insulin resistance was assessed using the homeostatic model assessment–insulin resistance (HOMA–IR). Abdominal adipose tissue distribution was determined by single-slice computed tomography at the umbilical level.

The investigators found that PI-treated children had significantly higher total cholesterol (p= 0.0021), LDL-cholesterol (p= 0.019) and triglycerides (p= 0.0018). Serum glucose, insulin, proinsulin and C-peptide, the insulin: glucose ratio, insulin resistance, estimated by the homeostatic model assessment-insulin resistance (HOMA–IR) and abdominal adipose tissue distribution were similar in both groups.

They reported that viral load, CD4 cell count and stavudine therapy were not significantly associated with serum lipids, insulin resistance or abdominal adipose tissue distribution. The strongest predictor associated with fasting serum insulin and HOMA–IR was the Tanner stage, which is the most widely used clinical scale for assessing pubertal development. Age was the most significant predictive variable of the visceral: subcutaneous adipose tissue ratio.

The investigators concluded that in this cohort of predominantly prepubertal HIV-positive children "PI therapy was associated with an atherogenic dyslipidemia but not with insulin resistance or abnormal abdominal adipose tissue distribution." and that "the results suggest that children, particularly prepubertal children, are less susceptible than adults to PI-induced changes in glucose homeostasis and abdominal adipose tissue distribution." They also write "…routine monitoring of serum lipids in all HIV-infected children, particularly those receiving PI therapy, is warranted."

Ref: Bitnuna A, Sochettb E, Babync P et al. Serum lipids, glucose homeostasis and abdominal adipose tissue distribution in protease inhibitor-treated and naive HIV-infected children AIDS 2003, 17:1319–1327

C O M M E N T

This is a useful study that may add to the arguments in favour of PI-sparing regimens for children. However, we do not yet know the long-term implications of the raised lipids for children.

Non-invasive methods of monitoring such as flow-mediated dilation in coronary and brachial arteries which correlates with endothelial dysfunction may be useful.

[Takase B, Uehata A, Akima T, et al. Endothelium-dependent flow-mediated vasodilation in coronary and brachial arteries in suspected coronary artery disease. Am J Card. 1998; 82: 1535-9]

HEPATITIS COINFECTION

Hepatitis A vaccine provides affordable protection in HIV-positive individuals

The use of an inactivated hepatitis A (HepA) vaccine provides affordable protection against HAV infection, which may be of particular importance in those who are HIV-infected. One of the inactivated HepA vaccines, HAVRIX, is highly immunogenic in non HIV-infected adults, resulting in seroconversion in up to 90% to 94% and 100% of persons after the first and second doses, respectively, of vaccine.

However, antibody responses to HepA vaccine are lessened in patients with HIV infection. The researchers examined whether two doses of vaccine, administered six months apart, adversely affected CD4 cell counts, plasma HIV RNA levels, or the clinical course of HIV-infection.

A total of 270 adults were screened, 133 of whom were HAV seronegative and enroled in the study (mean age, 38 years; range, 22-65 years). Of the 68 subjects (51.1%) who were randomly assigned to receive HepA vaccine, 48 (70.6%) completed the nine-month study. Of the 65 (48.9%) who received placebo, 51 (78.5%) completed the study. Sixty-two patients (91%) in the vaccine group were receiving antiretroviral therapy at the time of entry to the study, compared with 60 (92%) in the placebo group.

The overall frequency of seroconversion among subjects receiving vaccine was 49% at month seven and 52% at month nine. Among patients with baseline CD4 cell counts of 200-499 or greater than or equal to 500 cells/mm^3, seroconversion was observed in 53% and 73% at month seven and in 69% and 67% at month nine, respectively. After the first dose of vaccine, seroconversion at month six was observed in only four (13%) of 31 subjects with CD4 cell counts greater than or equal to 200

cells/mm“ and in no subjects with CD4 cell counts less than 200 cells/mm“.

The authors found no transient increases in plasma HIV loads after administration of HepA vaccine on HIV RNA levels. Increases in CD4 cell counts and decreases in HIV loads were observed in both subject groups throughout the study. Furthermore, the study demonstrated that the frequency of seroconversion and the magnitude of the resulting antibody titer varied significantly, depending on the initial CD4 cell count.

The authors conclude: “HepA was well tolerated and had no apparent effect on the course of HIV infection or plasma HIV RNA levels. Approximately two-thirds of our patients responded to two doses of vaccine administered six months apart. Compared with uninfected persons and with the results of other studies of HIV-infected persons, this relatively lower response rate was unexpected and remains unexplained.... Clinicians may wish to counsel patients that vaccination may not provide uniform protection against HAV. Whether vaccine response can be improved by the use of adjuvants or a third dose of vaccine or by delaying vaccination until there is evidence of improvement in the immune system in response to more highly active antiretroviral therapy, deserves further study.”

Ref: Kemper CA, Haubrich R, Frank I et al. Safety and immunogenicity of hepatitis A vaccine in human immunodeficiency virus-infected patients: a double-blind, randomized, placebo-controlled trial. J Infect Dis. 2003 Apr 15;187(8):1327-31. Epub 2003 Mar 24.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12696015&dopt=Abstract

PEG-interferon alfa-2b plus ribavirin for treatment of CHC patients who failed or relapsed following interferon-based therapy

The role of PEG-Intron (pegylated interferon alfa-2b/ PEG) and ribavirin (RBV) therapy for patients with chronic hepatitis C (HCV) who have previously failed interferon (IFN)-based therapies is not fully known.

The objective of the current study was to compare the safety and efficacy of continuous weight-based (CONT) versus. categorical weight-based (CAT) PEG-IFN alfa-2b/RBV in patients who have failed to achieve sustained virologic response after previous IFN/RBV treatment.

This is an open-label, multi-centre, randomised clinical trial of CONT vs. CAT PEG/RBV. Patients were randomised to receive 800mg RBV QD with either continuous weight adjusted PEG-IFN aldfa-2b (1.5 mcg/kg) QW (n=259) or categorical weight adjusted PEG-IFN alfa-2b (100 mcg if < 80kg, 150 mcg if > 80kg) for 48 weeks. HCV RNA was evaluated at baseline (BL), week 12 (EVR), and end of treatment (EOT). Intent-to-treat response rates were compared using Fischer’s Exact Test and logistic regression.

517 patients were enrolled and took at least one dose of drug. The median age was 47 years, and the patients were 64.8% male, 76.8% Caucasian, 13.5% Black and 8.3% Asian. HCV Genotype 1, 90.5% and 2 or 3, 9.5%.

Two hundred and seven patients completed 48 weeks of treatment. Two hundred and seventy-eight patients withdrew before EOT; the primary reason for withdrawal was viral non-response.

No differences were observed in AEs between treatment groups, including neutropenia (p=0.7). EVR/EOT for CONT and CAT were 40.0%/24.3% and 31.0%/25.6%, respectively (p=0.47 and 0.64)). EVR/EOT for relapsers and non-responders were 50.6%/34.9% and 23.9%/20.3%, respectively (p < .0003). EOT response was 23.8% in genotype 1 and 36.7% in genotype 2/3(p=0.046).

Conclusions: continuous and categorical weight-based dosing of PEG-IFN alfa-2b/RBV had similar safety and efficacy in the re-treatment of patients who failed or relapsed after original IFN-based therapy for HCV.

Among non-responders to prior therapy, the EOT response was more than 20%; as expected the EOT was higher among relapsers.

These data suggest that PEG-IFN alfa-2b/RBV may be effective in persons who initially failed to respond to or relapsed after previous IFN/RBV treatment.

Ref: M Sulkowski et al. PEG-interferon alfa-2b + ribavirin for treatment of patients with chronic hepatitis C who have previously failed to achieve a sustained virologic response following interferon alfa or interferon a-2b + ribavirin therapy. Abstract T1292 (poster). *Abstracts of Digestive Disease Week 2003*. May 17-22, 2003. Orlando, FL.

Source: HIVandHepatitis.com

C O M M E N T

Although sustained responses are awaited, these early data suggest that in previous Interferon +/- ribavirin non-responders, up to 20% may achieve end of therapy responses. Although this may not translate into sustained response, as shown by the study below, these

patients will gain benefit in terms of HAI score improvement.

Perhaps of slight concern from this study is the end of therapy responses in relapsers. This study suggests that only 50% of those who had all, by definition, had end of therapy response to previous interferon +/- ribavirin will achieve the same with re-treatment with PEG-IFN and ribavirin.

This suggests that for half of these patients, previous non-sustained response may in some way have rendered them unresponsive to further interferon-based treatment.

While we await the final data, further analysis of the viral genomic characteristics of these patients will be of interest in determining whether interferon therapy selects for, or induces viral resistance.

Pegylated interferon plus ribavirin improves fibrosis in non-responders to standard interferon therapy

Brian Boyle MD, HIVandHepatitis.com

Approximately 60% of the patients who are treated with Rebetron (standard interferon + ribavirin) fail to respond to that therapy. The re-treatment of this population, with a more effective regimen, for example pegylated interferon plus Rebetol (ribavirin), is primarily for the possibility of viral eradication, but even if that goal is not attained, secondary benefits may include biochemical or histological improvement.

In a study presented at Digestive Disease Week 2003, 193 patients who were virologic non-responders to Rebetron therapy were treated with PEG-Intron (pegylated interferon alpha-2b) plus Rebetol and evaluated regarding histologic improvement with that therapy. Of the enrolled patients, 160 were HCV genotype 1. After enrolment, the patients were randomised to receive either PEG-Intron 1.5 mcg/kg/week plus Ribavirin 800 mg/day or PEG-Intron 1.0 mcg/kg/week plus Ribavirin 1000-1200 mg/day for 48 weeks.

The investigators found that of 49 patients with paired liver biopsies after finishing 48 weeks of treatment, 17 (35%) were HCV RNA negative and 32 (65%) were HCV RNA positive. In these patients, the overall Histological Activity Index (HAI) improved after treatment from 5.91 to 4.47 and the fibrosis score improved from 2.65 to 2.22.

As shown in the table below, while the HAI significantly improved in both virologic responders and nonresponders, histologic improvement in fibrosis was significant only in patients who achieved an undetectable HCV RNA by the end of treatment.

	HCV RNA Negative at Wk 48			HCV RNA Positive at Wk 48		
	Pre-Treatment	Post-Treatment	p value	Pre-Treatment	Post-Treatment	p value
HAI	5.29 ± 2.1	3.35 ± 1.9	0.0008	6.25 ± 2.3	4.97 ± 2.4	0.019
Fibrosis	2.65 ± 1.2	2.12 ± 1.36	0.029	2.66 ± 1.1	2.28 ± 1.4	0.064

The authors conclude: “Significant histologic improvement was only seen in patients who achieved viral clearance by week 48. Patients that were PCR positive at week 48 achieved significant improvement in hepatic inflammation but not in fibrosis. Combination of Peg-Intron and Ribavirin is very effective in improving histologic activity in patients who failed to clear HCV RNA.”

Ref: K Selim et al. Histological improvement in patients with pegylated interferon alpha-2b plus ribavirin who were previously non-responders to Rebetron. Abstract 217 (oral). Abstracts of Digestive Disease Week 2003. May 17-22, 2003. Orlando, FL, USA.

Source: HIVandHepatitis.com
http://www.hivandhepatitis.com/2003icr/DDW2003/docs/052803f.html

DIAGNOSTICS

Rapid HIV testing - controversy in the US - and access in the UK

The recent availability of more rapid HIV tests has suggested that their introduction could reduce the numbers of people who fail to return for results, which in the UK may vary from 35% - 95% depending on clinic and risk group of the person being tested.

The new technology has increased the possibility for testing out of routine clinic settings and this in turn has also initiated debate about the counselling and support protocols that were developed in the 80s. The context for the following article from the Boston Globe, is the introduction of pilot studies using rapid testing in public settings in Seattle.

CDC recommendations

In April, The US Centres for Disease Control and Prevention (CDC) released a revised HIV/AIDS prevention strategy, which targets the estimated 200,000 people in the United States who are HIV-positive but are unaware of their status. The agency urged local health departments to use the rapid HIV test — which was approved by the FDA in November 2002 for use in about 40,000 hospitals and clinics with laboratories — in all federally funded clinics, as well as places such as homeless shelters, jails and substance abuse treatment centres.

In February, President Bush announced expanded availability for OraSure Technologies' OraQuick HIV test, which offers results that are 99.6% accurate within 20 minutes, to more than 100,000 doctors' offices and public health clinics. AIDS groups had advocated making the test more widely available to the general public. The CDC also recommended simplifying the pre-test counselling process. However, the CDC does not yet have recommendations on the use of the rapid test or what type of counselling should accompany the test, leaving such decisions up to local health authorities.

Working in counselling

The speed and portability of the new HIV test means that some people may find out they are HIV-positive in places where counselling and other services may not be immediately available, Fred Swanson, executive director for Gay City Health Project, said. Local health officials say that they can successfully combine counselling and testing in public locations.

The health department has drafted its own protocols for using the rapid test. "Our big challenge, and one of the big goals for the Centres for Disease Control, is to try to increase the number of people with HIV infection who know that," Chaffee said, adding, "One, because people who have HIV and don't know it are losing the benefits of good medicine. ... And two, we know from a variety of studies that when people know they have HIV infection, they are much more careful with their sexual and needle-sharing partners."

Although Washington state law requires pre- and post-test counselling, the law is not specific as to what the counselling should entail, according to the Globe. "Are recipients of positive test results going to be able to internalise the information they've received around the (new) test when they don't have any time to mull the information over?" Paul Feldman of Seattle's Lifelong AIDS Alliance asked. Swanson said that although he is worried about possible negative effects of using the rapid test in public settings, he said that he is reassured by the fact that the rapid testing will not occur immediately in gay bathhouses and sex clubs. "What's exciting to me is that the local health department recognizes that there may be some challenges, and as such is doing a trial run," he added (Boston Globe, 5/30).

Source: Kaiser Daily HIV/AIDS report
http://www.kaisernetwork.org

http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=18002

Boston Globe
http://www.boston.com/globe/

Quality Assurance Guidelines for testing using the OraQuick Rapid HIV-1 Antibody Test has just been published on the HIV/AIDS Prevention web site. This PDF document is available at
http://www.cdc.gov/hiv/rapid_testing/materials/QA_Guidlines_OraQuick.pdf

The document's appendices, which discuss government regulations and provide sample forms, are available at
http://www.cdc.gov/hiv/rapid_testing/materials/QA_Guidelines_OraQuick_Appendix.pdf

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C O M M E N T

Rapid tests have been available for several years in the UK (Determine, Abbott) and it is not clear why they still have not been more widely adopted - even though the unit cost is very low.

The test produces a result within 20 minutes from a fingerprick or plasma sample allowing patients to receive a result within an hour. This minimises the stress associated with the delay of receiving results which in the UK still routinely take up to a week. This should increasing uptake and impprtantly also increse the percentage of people who return for their results. Again in the UK, this can vary from less than 40% to 95% return rate depending on clinic, but improving must surely help government guidelines.

Although receiving an HIV diagnosis is still a traumatic event, the medical reality has changed significantly from the 1980s when many testing protocols were first developed. From an individuals' medical perspective an earlier diagnosis allows both better medical intervention, including accurate detection of infection with drug-resistant virus.

From a public health perspective this reduces the risk of further infections, which may be largely driven by people unaware of their HIV status, and high viraemia associated with recent infections. Pre and post test counselling can still be provided in this setting, with people receiving an HIV-positive diagnosis more likely to benefit from more significant support.

Including HIV and hepatitis within the routine serology testing at GUM clinics, with HIV becoming an 'opt-out' rather than 'opt-in'test was the subject of a recent article in the BMJ:
http://bmj.com/cgi/content/full/326/7400/1174

HIV testing with results within an hour is already available in the UK in very few clinics (John Hunter, London Lighthouse, Victoria Clinic and Soho clinic for gay men). Pre-test counselling and offer of follow-up counselling is provided as required.

OTHER NEWS

First HIV-positive heart transplant – with two-year successful follow-up

Simon Collins, HIV i-Base

The 5 June edition of the New England Journal of Medicine includes a two-year follow-up report from the first successful heart transplant, in January 2001, in an HIV-positive individual.

The recipient was a 39-year-old research scientist who had been diagnosed HIV-positive in 1992 and his history of opportunistic infections including KS, gastrointestinal CMV, disseminated MAI and PCP. Nadir CD4 count was 0 cells/mm3 in April 1994.

Antiretroviral therapy included nucleosides only until 1995 and when the first protease inhibitors became available and CD4 count increased to 400 by 2000 with no additional OI complications.

Echocardiography in 1995 revealed an ejection fraction of less than 25%, which progressively fell to 10% by October 1999. Assessment included attributing dilated cardiomyopathy to previous use of daunorubicin treatment.

Viral load has been maintained <50 copies/ml since 1998 including throughout the transplantation and post transplant follow-up. CD4 count dropped to <50 cells/mm3 during the period immediately surrounding the operation, but did not result in recurrence of previous AIDS-related infections. Sensitive serial monitoring included PCR for HHV-8 (associated with KS).

The report notes that "the clinical course has been marked by frequent episodes of rejection (grade 0 to 3A), revealed by serial endomyocardial biopsies; these episodes have not been associated with haemodynamic changes and have been treated with intermittent glucocorticoids (the data are summarised in Table 1). Other complications after transplantation have included an exacerbation of gouty arthritis, recurrent anal condyloma, and the development in March 2002 of anaemia (hematocrit, 25%) that was initially attributed to distal esophagitis–gastritis on endoscopic examination in April 2002. The patient recently became transfusion-dependent, despite the resumption of erythropoietin therapy (Table 2), and currently requires transfusions of packed red cells every two to three weeks. However, he continues to work full-time and exercises regularly.

Notably, the HAART in this case is a full-dose ritonavir-based regimen, and even more surprisingly this continues today. The significant interactions with ritonavir and calcineurin antagonists used after transplantation required particularly careful adjustment.

Ref: Calabrese L, Albrecht M, Zackin R et al. Successful cardiac transplantation in HIV-1-infected patient with advanced disease, NEJM 2003;348:2323-2328

C O M M E N T

Access to, and more importantly successful results from, solid organ transplants have increased in the last five years, largely as a result of HAART therapy. HIV-positive people are no longer automatically excluded from life extending surgery because their lives are assumed to be too short to justify the costs involved.

Highest success rates have been reported with kidney transplants, and the growing success with liver transplants for people with ESLD caused by hepatitis C is still complicated largely by reinfection. Use of immune-suppressing drugs essential in all transplants do not appear to present increased risks for HIV-positive patients compared to people who are HIV-negative so long as they have a minimal baseline CD4 count (currently >200 cells/mm3 for kidney and >100 cells/mm3 for liver transplants).

Drug treatment likely to be based on biased evidence

Drug treatment is likely to be founded on biased evidence because drug companies tend to publish studies with more favourable results, suggest researchers in the BMJ.

They identified 42 studies submitted to the Swedish drug regulatory authority to secure marketing approval for five antidepressant drugs. These studies were then compared with studies actually published between 1983 and 1999.

They found evidence of three sources of bias: duplicate publication, selective publication, and selective reporting. For instance, 21 studies contributed to at least two publications each, and three studies contributed to five publications. Studies showing significant effects of a drug were published as stand alone publications more often than studies with non-significant results. The tendency to report the more favourable results only, in studies actually published, was a major cause for bias.

These results should not be used to dispute the value of analysing the medical literature, say the authors.

However, they are likely to be valid for other classes of drugs, so for anyone who relies on published studies alone to choose a specific drug, they should be a cause for concern.

Without access to all studies (positive as well as negative, published as well as unpublished) any attempt to recommend a specific drug is likely to be based on biased evidence, they conclude.

Source: BMJ press release
http://bmj.com/cgi/content/full/326/7400/1171

ON THE WEB

A guide to the best new reports and resources posted on the internet

Conferences and workshop abstracts and reports:

FCHR: Therapeutic Vaccines Workshop

Slides of all presentations from the workshop organised by the Forum for Collaborative HIV Research from 24-25 April, 2003 are now available online:

http://www.hivforum.org/projects/therapeutic-vaccines.html

FCHR: Cardiovascular risk in HIV infection and treatment

Slides of all presentations from the workshop organised by the Forum for Collaborative HIV Research on 22 May 2003 are now available online:

http://www.hivforum.org/

Fertility regulation and systemic hormones in HIV-infected and at-risk women

Slides from more than 30 presentations from the workshop organised in McLean Virginia from 13-14 January 2003 are now available to download as pdf files. [Note you will need to download a pdf file of the programme as a guide to presentations, as the website only lists the files by individual author]

http://www.blsmeetings.net/1729/

Access issues:

Interview with Zachie Achmat

http://allafrica.com/stories/200305290027.html

Achmat and the Treatment Action Campaign (TAC) have led the campaign on the streets, in a bid to force a change in government policy on the treatment of HIV/Aids.

WHO and HAI launch new pricing study

The World Health Organization (WHO) and Health Action International (HAI) announce the release today of Medicine Prices, a pricing manual outlining how to collect and analyse data for 30 widely-used medicines.

Email the Documentation Centre at WHO EDM to obtain a copy:

edmdoccentre@who.int

Data from the pilot studies will be available on HAI's web site:

http://www.haiweb.org/medicineprices>www.haiweb.org/medicineprices

Indian drug-maker leads the charge for low-cost AIDS drugs

amfARs 'Treat Asia' – March 2003

http://www.amfar.org/cgi-bin/iowa/asia/news/index.html?record=3

Interview with Cipla CEO Yusuf Hamied

Predicting the public health impact of antiretrovirals: preventing HIV in developing countries

Researchers from UCLA and Harvard Medical School argue, that antiretrovirals should be considered as a prevention tool and not simply as a therapeutic tool.

Sally M. Blower and Paul Farmer. Full-text:

http://aidscience.org/Articles/AIDScience033.asp

Online medical lectures:

The Biology, Laboratory and Clinical Implications of Immune Activation and CD38 Expression in HIV Disease

http://hivinsite.ucsf.edu/InSite.jsp?page=cfcd38-00-00

Where's the AIDS Vaccine?

Laurence Peiperl, MD, UCSF

http://hivinsite.ucsf.edu/InSite.jsp?page=md-rr-17

Mucosal Immunity to the Rescue?: The Cellular Immune Response to HIV at Mucosal Surfaces

Barbara L. Shacklett, PhD, UCSF

http://hivinsite.ucsf.edu/InSite.jsp?page=cfwcp-02

Medscape articles:

From: AIDS Reader

Where Now for Trizivir? - Role of the Triple-NRTI Pill Post-ACTG 5095 - Graeme J. Moyle, MD, MBBS

Triple NRTI therapy should be avoided as sole initial therapy.

Histoplasmosis in a patient with AIDS

http://mp.medscape.com/cgi-bin1/DM/y/hb860F74sn0D1P0Faxk0AS

Long-term complications of nucleoside reverse transcriptase inhibitor therapy - Douglas Dieterich MD

http://mp.medscape.com/cgi-bin1/DM/y/hb860F74sn0D1P0FaxI0AT

Review of the major long-term complications associated with NRTIs: hyperlactatemia and lactic acidosis/hepatic steatosis, other hepatotoxicities, pancreatitis, lipodystrophy/lipoatrophy, neuropathy, and haematologic toxicities.

F*rom: American Journal of Clinical Pathology*

Toxic effects of nucleoside reverse transcriptase inhibitors on the liver

http://mp.medscape.com/cgi-bin1/DM/y/hb860F74sn0D1P0Faxj0AR

The authors demonstrate that NRTI-induced toxic effects in the liver may occur as indolent nonspecific disease with variable histologic features and emphasises the diagnostic value of electron microscopy, particularly when diffuse steatosis is absent.

Newsletters and reports:

IAPAC Monthly

http://www.iapac.org/iapacmonthly.asp?catid=14

June 2003 includes:

- Atazanavir gets FDA Advisory Committee's thumbs-up
- 31% of African TB now due to HIV epidemic
- NIAID comments on AACTG Study A5095
- Time to scale up the fight against AIDS in Europe

May 2003 issue includes:

- Retro Part 2: Heartbreaks and STIs
- Retro Part 2: Lopinavir's metabolic effects in men without HIV
- Retro Part 2: Some renal risk with tenofovir?

April 2003 includes:

- Retro Part 1: A suite of new therapies (or, my funny valentine)

March 2003 includes:

- How HIV voluntary testing can contribute to TB control
- About Tuberculosis
- Smallpox vaccination and the patient with HIV/AIDS

Coinfection:

Hepatitis coverage from the Digestive Disease Week Conference

May 17-22, 2003, Orlando Florida

Two websites contain coverage from this US meeting.

HIVandHepatitis.com:

http://www.hivandhepatitis.com/2003icr/DDW2003/main.html

NATAP:

http://www.natap.org/2003/DDW/ndxDDW.htm

Vaccine research:

Can DNA vaccines get a boost from cytokines?

IAVI Report - February/April 2003

Mark Boaz and Richard Jefferys

http://www.aegis.org/pubs/iavi/2003/IAVI2003-0203.html

Report from the annual Keystone conference on HIV Vaccine Development (28 March-4 April 2003, Banff, Alberta).

Headline stories reported from three corporate players: VaxGen, which discussed results from its recently completed Phase III trial; Merck, with updates on its Phase I clinical trials and announcing a new partnership with Aventis Pasteur; and Wyeth-Aherst, describing a strategy that may improve the usefulness of DNA-based vaccines.

Other news:

New PENTA website

The European paediatric trials network PENTA has a new website:

http://www.pentatrials.org

HIV infection and oral sex

Laurence Peiperl, MD, and Tom Coates, PhD

Detailed transcription from a roundtable discussion assessing the evidence on the risks of HIV infection from oral sex.

http://hivinsite.ucsf.edu/InSite.jsp?page=pr-rr-05

BMJ Press releases

Five press releases of general interest to trial reporting, and industry roles with doctors and community, with links to related articles in BMJ No 7400 Volume 326. All BMJ site articles are free in full text.

http://bmj.com/content/vol326/issue7400/press_release.shtml

1. Concern that research sponsored by drug companies is biased
2. Drug treatment likely to be based on biased evidence
3. Weekly contact with drug reps linked to unnecessary prescribing
4. Medical profession attempts to “clean up” relations with drug industry
5. Relations between the drug industry and patient groups should be open

MEETING ANNOUNCEMENTS

5th Workshop on Lipodystrophy and Adverse Drug Reactions and Lipodystrophy in HIV

8–11 July 2003, Paris, France.

http://www.intmedpress.com/lipodystrophy

Community Forum at IAS

A community forum organised by TRT-5 will take place on Sunday 13 July from 10 am to 5 pm at the Palais des Congrðs of Porte Maillot, Paris.

For further details please contact Véronique Collard:

collard@trt-5.org

2nd IAS Conference on Pathogenesis and Treatment of HIV/AIDS

13-16 July 2003. Paris, France

http://www.ias2003.org/

Forum for Collaborative HIV Research: Sex and Gender Issues in HIV

15 July 12-1:45pm

Room 252 AB, Le Palais des Congrès de Paris

Sex and gender issues impact HIV disease and its management at all levels, ranging from transmission to clinical disease manifestations, and including access to care and clinical research, prevention, as well as treatment related issues.

This lunchtime workshop will summarise the discussions and proposed research agenda set at the Washington workshop.

EACS Advanced HIV Course

27-29 August 2003

The European AIDS Clinical Society will organise its first course on Antiretroviral Therapy and Comprehensive Care for people living with HIV/AIDS, focused on the clinical management of HIV, in Montpellier (South of France), from 27-29 August 2003.

The application form can be download it from the EACS website.

http://www.eacs.ws>www.eacs.ws

For further information contact Sylvie Chatelin at the EACS Office, Tel : 33 1 44 24 17 96

sylvie-chatelin@psl.ap-hop-paris.fr

PUBLICATIONS AND SERVICES FROM i-BASE

Treatment Passports

This new, handy booklet from i-Base is for HIV-positive people – whether newly diagnosed or positive for a long time - to keep a record of their own health and treatment history.

Such a record is useful when talking to different health care workers, changing clinics and changing treatments. Like all i-Base publications, it is available free as single copies or in bulk.

Copies are being distributed with this issue of HTB and further copies can be ordered using the fax-back form also distributed with this issue, using the form on the back page or by visiting our website (details below).

Guide to Changing Treatment – now in Greek

Our guide to second line and salvage therapy has now been translated into Greek by the Athens-based organisation Synthesis. You can download the pdf file from our website (see below).

Further information in Greek is available at the Synthesis site:

http://www.hiv.gr

The information was updated January 2003. Our 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.

For additional free copies, including bulk orders see below.

Guide to Avoiding and Managing Side Effects - now in Italian

The i-Base Guide to Side Effects has now been translated into Italian by colleagues in Milan. You can download the pdf file from the i-Base web site (details below).

This is 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.

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

UK-Community Advisory Board: new reports and presentations

The UK-Community Advisory Board (UK-CAB) is a network for community treatment workers across the UK. Each meeting includes two training lectures and a meeting with a pharmaceutical company.

The programme, reading material, reports and powerpoint slides from the presentations from the fifth meeting, held on 2 May, are now posted to the i-Base website.

This meeting focused on:

- Access to treatment for UK visitors, refugees and asylum seekers - *Linda McDonald*
- TB and HIV coinfection - *Dr Anton Pozniak*
- T-20 - meeting with Roche

http://www.i-base.info/ukcab/may03/index.html

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

Genetics, resistance and HIV – *Professor Clive Loveday*

Approaches to Salvage Therapy – *Dr Mike Youle*

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

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

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

The i-Base web site

Our web address is:

http://www.i-Base.info

More than 500 people a day visit the site, where you can read all i-Base publications, fill in our readership survey, find details of the UK Community Advisory Boards (UK-CABs), learn about the organisation, our phone service and meetings, and access our archives and an incomparable range of links.

The site can also be used to order publications and regular subscriptions to be delivered by post or email (as pdf files).

Translations of 'Introduction to Combination Therapy'

This essential non-technical patient guide to combination therapy has been translated into Portuguese, Latvian and Slovak, by HIV-positive support organisations in those countries. The Portuguese version is available to download as a pdf file and reprint from the i-Base website.

For Latvian and Slovak copies please contact the i-Base office.

Printed versions of this booklet are also available in English, French, Italian, Spanish, Chinese and Macedonian.

The guide 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.

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 in a printed version, by pdf file and on our website:

http://www.i-base.info

The printed version is available at most HIV clinics in the UK and is available free by post: see below for details.

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Copies of publications can also be ordered by post or fax. These methods of ordering are suitable for all our publications: HIV Treatment Bulletin (HTB), Positive Treatment News (PTN) and all our treatment guides and reports.

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Changing Treatment - Guide to Second-line and Salvage Therapy *(January 2003)*

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Positive Treatment News (PTN) *from Spring 2003*

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