Volume 3 No.7 - AUGUST / SEPTEMBER 2002

SPECIAL ISSUE : CONFERENCE REPORTS from XIV INTL. AIDS CONFERENCE, Barcelona, and XI INTL. HIV DRUG RESISTANCE WORKSHOP, Seville,

CONFERENCE REPORTS:
THE XIV INTERNATIONAL AIDS CONFERENCE, Barcelona, 7-12 July 2002
TREATMENT ACCESS AND THE GLOBAL RESPONSE TO THE EPIDEMIC
• Bill Clinton and Nelson Mandela promise to lead peer education among political leaders as world looks for $10 billion a year to fight HIV/AIDS
• South African activist unveils campaign to force compulsory licences
• MSF study shows treatment in resource-poor settings is effective
• ‘Barcelona Declaration’ demands 2m poor people are treated in the next two years
• Lives were lost as experts argued the merits of care versus prevention, says Stefano Vella
• Peter Piot sets out the global political agenda in the fight against HIV/AIDS
• Health should be a right, not a commodity, and medicine must be removed from the World Trade Organisation, argues key speaker
• Governments must act to cut drug prices, says Kenya’s health minister
• Civil society had to fight for universal access to AIDS drugs in Brazil
• Coalitions of local NGOs can effectively demand access to medicines, reports MSF
• Involvement of PLWHA is key to improving access to treatments
• ART can successfully tackle advanced disease in resource poor settings, reports MSF
• Investment in treatment and care significantly reduces company health and social expenditure in Abidjan
• Financing the global response to the epidemic will cost $9.2 billion a year, according to one estimate
• The Global Fund: what, where, how much?
• Leading businesses spurn Global Fund
• 14 Caribbean governments sign cut-price drugs agreement with six pharmaceutical companies
• Thailand offers low-cost transfer to African countries of technology for the local production of generic antiretrovirals
• Informal market plays a role in distributing antiretrovirals but exposes clients to several risks
• The epidemic in numbers

CLINICAL SCIENCE
• Abacavir hypersensitivity reactions in patients who rechallenge after interruptions for reasons other than hypersensitivity
• Prolonged CNS side-effects of efavirenz can be severe and lead to treatment discontinuation
• Paediatric reports at ICA 2002
• Study of MTCT programme finds resistance in women on two doses of monotherapy
• Emergence of resistance in children treated with ddl/d4T after treatment to reduce MTCT
• Correlates of fatigue in HIV disease
• Optimum hydroxyurea dose determined

contents continued on page 2...
Management of treatment experienced patients
Pharmacokinetics and therapeutic drug monitoring (TDM)
HIV-associated malignancies in the HAART era: flickers of hope and understanding
Lopinavir/ritonavir exhibits sustained virologic response in antiretroviral-naïve patients: 3-year data
Patients will have options regarding T-20 (Enfuvirtide) injection sites
The role of tenofovir in antiretroviral-naïve patients
Treatment interruption strategy reports from the XIV International AIDS Conference
New data from clinical trials of antiretrovirals
EFAVIP-2 Study
IMMUNOLOGY AND BASIC SCIENCE
Behind the headlines about vaccine research
Short resistance reports from Seville
New anti-HIV compounds discussed at the Seville HIV Drug Resistance Workshop and the Barcelona World AIDS Conference
Review of phenotypic resistance testing data presented at the XI International HIV Drug Resistance Workshop
ANTIRETROVIRALS
Trial supports lopinavir/ritonavir as first-line therapy in HIV infection
Ritonavir has anti-neoplastic effects independent of HIV inhibition
Antiretroviral use in pregnancy and the risk of an adverse outcome
METABOLIC TOXICITIES AND SIDE EFFECTS
Triglyceride increase can predict lipodystrophy in HIV patients under highly active antiretroviral therapy
Peripheral neuropathy: New data on risk factors, incidence and association with viral load
High prevalence of osteonecrosis of the hip found in HIV-infection
PATHOPHYSIOLOGY
Gene discovery offers fresh perspective on HIV/AIDS therapies
Growth hormone effective in increasing thymic activity
HIV long term nonprogressors have increased immune responsiveness to other viral pathogens
Red blood cells new sensitive markers for HIV disease progression?
PAEDIATRICS
Increased risk of heart abnormalities in children born to mothers with HIV-1
OPPORTUNISTIC INFECTIONS
Paclitaxel effective for advanced AIDS-related Kaposi Sarcoma
MISCELLANEOUS
Study finds sexual dysfunction common in HIV-infected men receiving HAART but unrelated to protease inhibitors
ViroLogic announces launch of “viral fitness” assay for HIV infection
OTHER NEWS
Investigations fault HIV/AIDS cure claims
US antitrust case could break GlaxoSmithKline’s hold on key drugs
ON THE WEB
Adherence research roundup from the International AIDS Conference
Highlights of presentations on gender from Barcelona
Additional ICA2002 reports at thebody.com
Medscape conference coverage, based on selected sessions at the: XIV International AIDS Conference
Selected daily updates from the XIV International AIDS Conference at HIVandHepatitis.com
NATAP reports from AIDS 2002 Barcelona
Monkey puzzles
Diversity considerations in HIV-1 Vaccine Selection
Confronting the limits of success
Mycobacterium avium complex and atypical mycobacterial infections in the setting of HIV infection
Management of anal and cervical dysplasia in men and women
Presentation
Anaemia, neutropenia, and thrombocytopenia: pathogenesis and evolving treatment options in HIV infected patients
Identifying and managing morphologic complications of HIV and HAART
Achieving adherence with antiretroviral medications for paediatric HIV disease
“Natural” resistance to HIV: Is the evidence good enough to design an effective vaccine?
Efficacy and safety of once-daily antiretroviral therapy
Therapeutic implications of acute hepatitis C infection
New antiretrovirals in development: The View in 2002
Update on IL-2: where it’s been and where it’s going
Insights into HIV-specific CD4+ T cell immunity
Updated knowledgebase chapters, Cytomegalovirus
The switching spiral: a triumph of hope over benefit
peripheral neuropathy
The push for once-daily HAART: a call for caution
Enhancing adherence to antiretrovirals: Strategies and regimens
High doses of riboflavin and thiamine may help in secondary prevention of hyperlactatemia
Conference Report, HAART and prevention of HIV transmission
PUBLICATIONS AND SERVICES FROM i-BASE
Updated edition of our guide to avoiding and managing side effects
The latest issue of Positive Treatment News (PTN)
Changing treatment: an updated guide to second-line and salvage therapy
Treatment information request service
Order i-Base publications via the internet, post or fax
CONFERENCE REPORTS
THE XIV INTERNATIONAL AIDS CONFERENCE
Barcelona, 7-12 July 2002

TREATMENT ACCESS AND THE GLOBAL RESPONSE TO THE EPIDEMIC

Bill Clinton and Nelson Mandela promise to lead peer education among political leaders as world looks for $10 billion a year to fight HIV/AIDS

Graham McKerrow, HIV i-Base

On the Thursday evening of the conference former US president Bill Clinton was asked at a “town hall meeting” to act as a peer educator to make other world leaders respond to the AIDS crisis. The next day he told perhaps 10,000 delegates at the closing ceremony: “I pledge that in every speech I make and in every meeting I have I will raise this and I ask you both to hold me accountable to that pledge and to tell me what more I can do.”

Speaking from the same platform as former South African president Nelson Mandela, Clinton added: “President Mandela and I have agreed to work together to launch the World Leaders AIDS Network … to raise the global commitment to end AIDS.”

The first 12 International AIDS Conferences were focused on the scientific work to develop treatments, and the 13th conference, two years ago in Durban, directed attention towards the need for political leadership to confront the AIDS crisis in developing countries. The 14th conference, held in Barcelona, Spain, in July, highlighted the need for world leaders to make sure there were sufficient resources to respond to the epidemic.

Most estimates put this at $10 billion a year. Some people said it was more like $25 billion.

Political leaders stayed away from the Durban conference as poor countries ignored their own problems, and the host, President Thabo Mbeki, was booed for questioning the link between HIV and AIDS.

This year countless presidents, prime ministers, former presidents and former prime ministers and ministers of health attended the conference. A list of just some of them appears at the foot of this article.

During the conference, Dr Denzil Douglas, the prime minister of St Kitts and Nevis, announced that he had signed an agreement on behalf of 14 Caribbean nations for the cut-price purchase of antiretroviral drugs from six pharmaceutical companies. For some of the supplies, the companies promised to match the lowest prices in the world.

Many debates included speeches from the platform or from the floor by serving ministers of health such as Sam Ongeri, the Kenyan minister of public health, and Assana Sangare, the AIDS minister for the Cote d’Ivoire.

But it was not only poor countries that were represented. Tommy Thompson, the US secretary of health, gave a speech, although it was made inaudible by shouts and whistles from protestors. A copy of his speech distributed afterwards said that America was doing more than any other country to combat HIV/AIDS, but he made no new promises.

The lobbying group Health GAP (Global Access Project) criticised the US for paying a smaller percentage of its GDP to the Global Fund for AIDS, TB and Malaria than were poorer nations like Uganda.

Health GAP led much of the protest at the conference and focused on companies like Anglo American, the largest mining company in South Africa, and Coca-Cola, demanding that they do more to provide access to treatments for staff in poor countries.

ACT-UP protesters trashed pharmaceutical company marketing stands in a routine manner that attracts less attention at each passing conference.

Several hundred people attended a rally and march on the eve of the conference, at which a ‘Barcelona Declaration’ was unveiled demanding donations of $10 billion a year for fighting AIDS around the world, antiretroviral (ARV) treatment for two million people in the developing world by the time of the International AIDS Conference 2004 in Bangkok, lower ARV drug prices in the developed world and universal access to drugs in the developing world by 2004.

One speaker at the end of the Durban conference said it had seen “activists become scientists and scientists become activists.” The Barcelona conference saw the political baton seized by an even more appropriate group: politicians.

Nelson Mandela walked onto the stage at the Palau St Jordi for the closing ceremony, supported by a walking stick in one hand and holding Clinton’s arm with the other.
Mandela said: “AIDS is killing more people than all the wars in history and natural disasters. AIDS is a war against humanity. This is a war that requires the organisation of entire populations.” And he said that there was a growing number of children being orphaned by AIDS, and added: “I ask all leaders of the world: is it acceptable? We know that there are treatments available to stop TB and help AIDS sufferers for several years at least but these parents had no access to treatments. Is this acceptable? The answer is no. We have to make this treatment available to everyone who needs it, regardless of their ability to pay.”

Mandela outlined three challenges for the world. The first was for all institutions, public and private, to make real and rapid progress on achieving access to treatment for all people who need it regardless of their ability to pay.

His second challenge was that testing should be available to all: “If HIV testing is not available free of charge you must demand it. It is your right to know.” He also said businesses should not humiliate people by testing them openly.

Mandela added: “My final challenge is to leadership. When leadership starts at the top it is more effective.” But he made clear this was not only a call to political leaders, but also to business leaders, trade union leaders, religious leaders and the leaders of NGOs.

He said: “I am calling on all leaders in the world today to ask themselves what they have done to limit the AIDS pandemic, and whatever they have done or not done, they must do more.”

At the end of his speech he spoke directly to political activists – as someone who has been an activist all his life. He said – “You have my greatest admiration. Keep on fighting and you will overcome.”

Clinton told an audience of 1,000 at the town hall meeting that the rich countries simply had to foot the bill for fighting the pandemic. He seemed to suggest a regional response would be appropriate when he said that the US and Canada should provide the money to enable the Caribbean to respond to the crisis, “to bridge the gap between the cost of treatment and what the countries can afford.” He said: “You should come to us and we should pay.”

And he urged countries to negotiate lower prices with the drug companies and said that if the deals offered by the companies were unsatisfactory they should buy from generic manufacturers in Thailand or India.

Clinton told the closing ceremony: “Developing countries have to work out how much they can pay and send the rest of us the bill for the difference.

“Leaders everywhere must move aggressively to remove stigma and denial. There are still people who think people living with HIV/AIDS are people who are different. Yes, they are sex workers, and poor and often gay men … but they are also our friends.”

Other politicians who addressed the conference included: Kim Campbell, former prime minister of Canada; IK Gujral, former prime minister of India; Paul Kagame, president of Rwanda; Pascoal Mocumbi, prime minister of Mozambique; Ali Hassan Mwinyi, former president of Tanzania; Jorge Sampaio, president of Portugal; Meechai Viravaidya, senator from Thailand and UN AIDS ambassador; Marcus Bethel, minister of health of the Bahamas; Henri Claude Voltaire, minister of health of Haiti; Jerome Walcott, minister of health for Barbados; Mrs Graca Machel, Southern African activist; Barbara Lee, US Congresswoman and Crispus Kiyonga, former minister of health for Uganda and now chair of the Global Fund to Fight AIDS, TB and Malaria.

Another speaker was The Most Reverend Njongonkulu Ndungane, archbishop of Cape Town and metropolitan of the Church of Southern Africa.

**South African activist unveils campaign to force compulsory licences**

Graham McKerrow, HIV i-Base

A treatment activist used a pre-conference satellite meeting in Barcelona to announce a campaign in the South African courts to force the introduction of compulsory licences to allow the local production of generic versions of antiretrovirals.

Sipho Mthathi of the Treatment Action Campaign (TAC) said that “in the next few months” they would initiate litigation to force the introduction of compulsory licences “so our government can buy treatment more cheaply.”

The legal action would follow TAC’s triumph a few days before the conference when the South African Constitutional Court instructed the government to provide treatment to pregnant women to help combat vertical transmission of the virus.

Compulsory licences are granted by national authorities, without or against the will of the title-holder, to allow the production of generic versions of drugs that would otherwise be protected by patents or other intellectual property rights.

Announcing the planned litigation, Mthathi added: “I am sure the pharmaceutical companies will be interested to learn about this!”

He said that treatment was “a right, not a favour” and called for “a strong Africanist movement” to advocate treatment in Africa. A pan-African conference in September would work out regional strategies to ensure access to essential medicines, he told the meeting.
Mthathi called for increased pressure on African governments to include HIV treatment in the New Partnership for Africa’s Development (NEPAD) “because there will be no development if Africa does not deal effectively with HIV/AIDS.”

The session, hosted by Médecins Sans Frontières and Health GAP (Global Access Project), heard about the success of litigation in other countries where governments have been forced to provide treatment for their citizens.

Erickson Chiclayo of Gente Positivo in Guatemala and the Network of Positive People Living in Central America, said there had been legal actions against governments, ministers of health and presidents, in countries such as El Salvador, Guatemala and Costa Rica “and thanks to these actions people are getting treatment now”.

“We have also carried out actions like closing streets to pressure for treatment for people with HIV,” he said. Action against the minister of health in Guatemala was stopped after the government agreed to treat 27 people. Since then, they have initiated legal action against the president of the country.

Chiclayo said that despite some success they still had a long way to go. He reported that in Belize 20 people were being treated out of the 400 who needed antiretroviral therapy. In Honduras, 400 were receiving ART, while 5,000 needed treatment. In Guatemala 1,600 were treated while 4,000 needed it and in El Salvador 500 people were on treatment while 4,000 needed it.

A speaker from Brazil said his country was often held up as an example of how a low-income country could treat its positive citizens with antiretrovirals, “but it is not an example because the government decided to do something,” he said. “It is an example because we pressured them into doing something.”

In response to the move by some pharmaceutical companies to give free or cheap drugs under certain conditions to a handful of countries, he said: “We don’t want donations. We don’t want gifts. We need treatment on a permanent basis.”

MSF study shows treatment in resource-poor settings is effective

Graham McKerrow, HIV i-Base

Médecins Sans Frontières (MSF) reported to a satellite meeting in Barcelona that a study of 1,000 people on treatment in resource-poor settings showed that the patients adhered well to regimens and the treatments were effective.

Jean-Michel Tassie from Paris described his analysis of people receiving treatment at MSF treatment programmes in Asia, Africa and Latin America. Fred Minandi a farmer from Malawi and one of the recipients of the free-to-user treatment told the meeting how much difference the treatment programmes made.

Tassie said that his analysis showed that after six months 93% of the patients studied were still alive and that 96% of those were still on treatment. He said his research showed individual benefit and good adherence to treatment, which was mainly combinations of NNRTIs.

Minandi told the meeting he had been ill for four years “but I am here thanks to the MSF treatment programme”. He said his visit to the Barcelona conference was his first trip outside Malawi, and he then spoke movingly about the problems his country faced.

“I am losing friends because they don’t want to talk about it. People in Malawi don’t want to know and that is why my country is dying in silence.

“Treatment is the best tool against stigma. When you are ill people see their own deaths in your eyes, but with treatment you look better and people are not so afraid.

“I would like to appeal to all the pharmaceutical companies to reduce the prices of their drugs for all the poorer countries,” he said.

‘Barcelona Declaration’ demands 2m poor people are treated in the next two years

Graham McKerrow, HIV i-Base

Several hundred people attended a rally and march on the eve of the conference, at which a ‘Barcelona Declaration’ was unveiled with four demands to extend treatment to millions more people in poor countries.

The demands were for:

- Donations of $10 billion a year for fighting AIDS around the world,
- Antiretroviral (ARV) treatment for two million people with HIV/AIDS in the developing world by the time of the International AIDS Conference 2004 in Bangkok;
- Lower ARV drug prices in the developed world and universal access to generic drugs in the developing world by 2004;
A new global partnership between governments and NGOs recognising the primary role of NGOs in the global fight against AIDS.

After the rally, a deputation of the organisers presented the declaration to Stefano Vella, the outgoing president of the International AIDS Society.

The main speaker at the rally was Dr Joep Lange, the incoming president of the International AIDS Society, who warned against the danger of waiting for a vaccine and in the meantime “leaving the problem unresolved and people untreated”.

Lange told about 600 demonstrators that the demand for $10bn was “a joke” and that up to $25bn was needed. However, he said that a Global Access Alliance was “in the making” to promote cooperation and avoid duplication.

US Congresswoman Barbara Lee told the rally: “I’m from Oakland, California, where we have a state of emergency in the African American community.” She said the problems were duplicated around the world and $10bn was “a drop in the bucket”.

Another speaker claimed the pharmaceutical company GlaxoSmithKline spent $500m a year on marketing “AIDS drugs”, a sum he said would pay to treat a million people.

The rally was organised by AIDS Therapeutic Treatment Now (ATTN), a new organisation with offices on Sunset Boulevard, Los Angeles. Some delegates boycotted the march and others attended another rally after a series of arguments over hostile language ATTN had used to describe some pharmaceutical companies and complaints that ATTN was too America-centric.

Lives were lost as experts argued the merits of care versus prevention, says Stefano Vella

Graham McKerrow, HIV i-Base

Time has been wasted – and lives have been lost – in the last two years because experts argued over whether prevention or treatment was the more pressing global need, Stefano Vella the president of the International AIDS Society, the conference organisers, said at the opening ceremony in Barcelona.

Vella told delegates that he thought the International AIDS Conference in Durban two years ago had been a success, but he added: “We then lost quite some time, and quite some lives, debating if it is better to bring more prevention or more care and treatment. I think that is now over because, as Peter Piot [executive director of UNAIDS] said recently, we finally understood that the quality of future lives depends on the quality of present lives.

“If we talk about preventing mother to child transmission, we cannot forget that we need the mothers and the fathers.”

Vella also criticised governments, although he welcomed the many government representatives present at the Barcelona conference.

He told them: “The International AIDS Conferences have never been the conferences of governments, particularly of the governments of the north, because in 20 years of AIDS history, with some exceptions indeed, governments have not been the driving force of this battle and have rather followed the wave according to their political agendas.”

His warmest welcome was reserved for scientists “not only because they invented the tools to fight HIV”, he said, “but also because I never saw in other fields of medicine this growing ‘scientific activism’ and the inclusion of the universal access to health care in the scientific agenda of the most relevant AIDS research institutions of the world.

“Indeed, scientists progressively understood that they should take the lead with the idea that the advancements of medicine cannot be reserved to small numbers of human beings.”

Peter Piot sets out the global political agenda in the fight against HIV/AIDS

Graham McKerrow, HIV i-Base

AIDS has entered a new era as a major issue on the global political stage, according to Peter Piot, executive director of UNAIDS, who set out the immediate political agenda when he spoke to thousands of delegates at the opening ceremony in Barcelona’s huge Palau St Jordi.

He said it was now important to mobilise the political commitment, to scale up the prevention and treatment work, eliminate stigma, develop a vaccine and find $10 billion a year to fight the virus.

Piot told his audience it now had to fight AIDS on the political stage “where struggles over power and resources are fought”. He said: “Governments promised leadership - all of them – at the UN General Assembly Special Session on AIDS [UNGASS] last year and in innumerable summits. The pharmaceutical industry must keep its promise to make AIDS drugs available to developing countries at affordable prices, and scientists to keep the promise to work where the real needs are, not just where the money and glory lie.”
He said 30 presidents and deputy presidents have made AIDS a priority by taking personal command of their national responses to the health crisis. He said the same was true of the presidents and prime ministers attending the conference.

“Their response signals a new era: the era of AIDS as a global political issue,” said Piot.

He addressed the politicians directly: “World leaders take note: success is possible. Prevention efforts in a growing number of developing countries clearly demonstrate that significant declines in HIV rates are possible. Antiretroviral treatment has slashed mortality in high income countries. Brazil has shown it can be done elsewhere.”

Piot asked why only 30,000 Africans were receiving antiretroviral therapy “when a hundred times that number need it” and why the world has failed to stop the dramatic expansion of HIV. The answer, he said, was about “power and priorities”.

“Treatment is technically feasible in every part of the world. Even the lack of infrastructure is not an excuse – I don’t know a single place in the world where the real reason AIDS treatment is unavailable is that the health infrastructure has exhausted its capacity to deliver it. It’s not knowledge that’s the barrier, it’s the political will.”

And he went on: “Ten billion dollars annually is all it will take for a minimum credible response to the epidemic. It is three times more than is available today. Every funder – governments, business, citizens and the new Global Fund need to get behind this target and start raising their share.”

“The world stood by while AIDS overwhelmed sub-Saharan Africa. Never again. We cannot stand by as passive observers while other continents repeat history, and we must not fail Africa now, in her attempts to turn back the epidemic’s devastation.”

Piot said the first “delivery date” for promises made in the UNGASS Declaration of Commitment is 2003. He said: “When this Conference gathers again in Bangkok [in July 2004] we will know who has delivered on the first UNGASS promises, due to be achieved in 2003.” He warned: “Bangkok will be a time of accountability.”

Piot said that fighting HIV in the future had to draw on the lessons of how it has been fought in the past: “Whenever and wherever we’ve succeeded against AIDS, it has been by challenging power and turning conventional wisdom on its head. Gay men and injecting drug users forced their way to the decision-making table. We have done it before, and now we must do it again.”

Health should be a right, not a commodity, and medicine must be removed from the World Trade Organisation, argues key speaker

Graham McKerrrow, HIV i-Base

Health should be regarded as a right not a commodity to be traded in the markets, delegates attending the conference's first plenary session were told by Dr Irene Fernandez, director of the Malaysian AIDS organisation Tenaganita and Chair of the Asian NGO umbrella organisation CARAM-ASIA (Coordination of Action Research on AIDS and Mobility).

She said the world was seeing a new paradigm in access to care with long-standing global iniquities being challenged.

“From disputes with the World Trade Organisation to court cases in South Africa, debate in relation to essential medicines has been resolved in favour of lower trade barriers to access.

“The principle of preferential pricing for HIV drugs for low- and middle-income countries has been largely accepted in the pharmaceutical industry. Prices have begun to drop and countries’ rights to invoke compulsory or voluntary licensing arrangements on patented drugs and on medications were affirmed clearly at the World Trade Organisation meeting in Dohar, Qatar, in late 2001,” said Dr Fernandez.

“But this is not enough. We need to go further and attack the root causes of the denial of treatment. Unless and until health is recognised as a fundamental right, any other interventions, like using funds from the Global Fund for drugs, becomes a dole out.

“In this context what we need to struggle for is to take health out of the World Trade Organisation. Health cannot be seen as a commodity any more. Health care must be available to all people, especially the poor.”

Dr Fernandez said responsibility and accountability for effective health care and access to treatment should be in the hands of governments and “not surrendered to transnational drug corporations”. Only if this happened, she argued, could national health policies evolve from the needs of the people, rather than as the consequence of market forces.

Dr Fernandez blamed the IMF and World Bank for pushing countries to privatise their health care services under structural adjustment programmes. “Consequently health care has been converted into a lucrative trade in people’s health. This system allows the health care industry to own and market the commodity.”

People who required health services had to purchase them through health insurance, said Dr Fernandez, but insurance was denied to HIV positive people. “It therefore not only marginalises people with AIDS, but denies them their right to treatment. Medicine, then, in the market place serves the demands of a few and follows its own commercial interests for pure profit.”
Drug patenting and profits kept prices high, she argued, which in turn prevented millions of people in the south from having access to drugs.

Dr Fernandez also criticised international trade and development policies that kept countries poor. She blamed the rich nations for insisting on free trade for developing countries while, for example, the United States gave its farmers subsidies worth $190 billion and Europe protected its farmers with $160 billion of subsidies.

In 1970, said Dr Fernandez, the countries of the Organisation for Economic Cooperation and Development agreed that 0.7% of their gross domestic products would be given in foreign aid, but the current official development assistance is only 0.22%. Dr Fernandez said this aid amounted to $53 billion today, when it should be $175 billion. “The G8 countries are continuously in default,” she concluded.

Dr Fernandez was giving the second Jonathan Mann Memorial lecture in memory of the first director of the Global programme on AIDS.


Governments must act to cut drug prices, says Kenya’s health minister

Graham McKerrow, HIV i-Base

Market competition will not lead to lower drug prices, Sam Ongeri, the Kenyan minister of public health, said in a dramatic intervention from the floor during a debate on strategies for lowering drug prices. Only government intervention could lead to cheaper treatments, he argued.

To loud applause he outlined how he had cut the cost of treatment from about $1,500 a year to just $300.

“In Kenya, we introduced compulsory licences and parallel imports and now we have cut three drug antiretroviral therapy treatments to $300.”

He said he “pushed laws through parliament” to allow parallel imports and compulsory licences. ‘Parallel imports’ are drugs imported from markets where they are cheaper because of local deals with the manufacturers or local production of generic versions. ‘Compulsory licences’ are issued by national authorities to allow local production of generics regardless of the views of the licence holder.

Ongeri said: “We will never get lower drug prices if we leave it to competition between the drug companies. We need government intervention.”

Civil society had to fight for universal access to AIDS drugs in Brazil

Graham McKerrow, HIV i-Base

Different social movements in Brazil united to press the authorities to provide universal access to treatments before the government would take action that has resulted in the country being held up as a model for others to follow, reported a speaker from the Brazilian Interdisciplinary AIDS Association.

Another speaker told a separate session that the production of generic versions of antiretroviral (ARV) drugs allowed universal access to the drugs and had resulted in an 80% reduction in the number of hospitalisations, cut the death rate and saved Brazil $222 million between 1997 and 2000.

Carlos André Passarelli, and colleagues from Rio de Janeiro, carried out a study of how Brazil achieved its much-admired treatment policies. [1]

They conclude that “the universal access guarantee is a continuous process of follow-up and improvement, which depends on the civil society’s involvement to uphold the social control” of Brazilian public health policy.

Passarelli said Brazilian laboratories started producing AZT in 1993 and two years later the ministry of health said the distribution of antiretrovirals (ARVs) was a state responsibility. The following year the 11th International AIDS Conference reported on the efficacy of drug combinations.

In 1999 Brazilian NGOs held demonstrations to demand state funding of ARVs. In 2001 the USA sued Brazil over their patent law and 39 pharmaceuticals filed suit to protect their licences in South Africa. The same year the World Trade Organisation (WTO) ministerial conference agreed that the TRIPS (the WTO’s Agreement on Trade-Related Aspects of Intellectual Property Rights) agreements would not override health requirements.

The researchers reported that Brazil’s history of activism, the characteristics of the Brazilian public health system and the local manufacture of AIDS drugs, all played their parts in achieving universal access to treatments. Also key factors in the success
were “the use and application of legal and constitutional mechanisms and the Brazilian government’s commitment to acquire and produce AIDS drugs”.

Passarelli said the social gains of the Brazilian ARV policy included a better quality of life for PLWHA and the commitment of PLWHA on prevention issues.

Celia Szwarcwald, professor of biostatistics at the Brazilian National School of Public Health, said Brazil was a low-income country with a GDP per capita of only $4,500 and a huge wealth gap. It is the unique low-income country to provide universal access to ARV therapy, a policy that has resulted in an 80% reduction in hospitalisations, she said, and has cut the number of deaths while the number of new cases continued to grow.

However, the cost of the drugs was a challenge to the Brazilian programme so, following the publication of evidence about the efficacy of combination therapy, the country stepped up production of generics.

Szwarcwald and colleagues conducted a mathematical analysis of the annual total cost of ARV therapy in the period 1997 to 2000. [2] They found a reduction of 72% in the average individual cost of dual therapy, and a reduction of 64% in the individual cost of triple therapy over the period.

They also found that despite the increasing number of patients, the total annual therapy costs decreased 8% from 1999 to 2000, and did not exceed the budget limit of £300 million.

Szwarcwald said the average cost of triple therapy was $17 a day in 1998 but that was reduced by 40% by 2000. The total ARV therapy bill for Brazil fell from $281 million in 1999 to $258 million the following year. The researchers calculated that generic production saved the country $222 million between 1997 and 2000.

She added: “The national production of ARV drugs has provided the basis of negotiations with drug companies.”

The researchers concluded: “As a result of the national production of generics, the cost of ARV treatment has not escalated in recent years, making it possible to maintain universal access to ARV therapy. The Brazilian model offers important lessons to developing countries, as it shows that universal anti-AIDS therapy is an achievable goal, even in a low-income country context.”

Another presentation showed that median survival of people with AIDS diagnoses was five months for patients diagnosed before 1989, 16 months in 1995, and 58 months in 1996. [3]

The researchers concluded: “Survival time has increased by over ten fold for adult Brazilian AIDS patients with the greatest improvement in recent years, coincident with universal HAART treatment.”

References:

Coalitions of local NGOs can effectively demand access to medicines, reports MSF

Graham McKerrow, HIV i-Base

National NGOs need encouragement to build coalitions to improve access to medicines, reported a team from Médecins Sans Frontières Holland (MSF-H). They reported on coalition building projects in Ukraine, Nigeria and El Salvador and said they can be effective in public action, political lobbying and coordinating local technical expertise.

Kevin Moody of MSF-H said their Ukraine programme tackled vertical transmission and treated infants. They have involved the All-Ukraine Network of PLWHA and found that different factions could unite over the issue of treatment.

In the delta region of Nigeria, said Moody, in 2000 they launched a coalition that included journalists, politicians and celebrities, as well as NGOs, to lobby for access to medicines in general.

In El Salvador MSF runs a mother to child transmission programme that imports medicines from Spain for use in and around San Salvador. MSF facilitated meetings of PLWHA and NGOs and were greatly helped because one strong NGO had a very charismatic leader.
Moody said their reasons for failure included oppressive governments, fragmented civil society and lack of training and information. The reasons for success included focusing on common goals, and support from other organisations. He said it was essential that NGOs were vital “and not searching for the next funding”.

MSF-H found that NGOs needed strengthening in all areas of management and Moody emphasised that coalitions had to be driven by local groups and supporters, not by outsiders.

“Northern NGOs must facilitate and support southern NGOs without taking over the coalition,” he said.


Involvement of PLWHA is key to improving access to treatments

Graham McKerrow, HIV i-Base

Many speakers at the conference emphasised the need for positive people to be involved in improving access to treatments, by applying political pressure on governments, by acting as peer educators to inform others about the treatments, and by organising treatment programmes.

A UK-based organisation presented evidence of the usefulness of involving positive people, a plenary session speaker called on communities to take the lead in demanding and providing treatment and an umbrella organisation of PLWHA organisations around the world presented proposals to treat 30,000 in Africa and the Caribbean.

Mandeep Dhaliwal of the International HIV/AIDS Alliance based in Brighton, UK, and colleagues have used the Handbook on Access to HIV Related Treatment, a collection of tools, information and other resources, to enable PLWHA groups to become more involved in improving access to treatment.

The handbook was developed by the Alliance with support from the World Health Organisation and UNAIDS and has been used by groups in India, Cambodia, Zambia and the Philippines.

Dhaliwal said PLWHA could improve services by making sure they were relevant to users, and other benefits included people being more informed, seeking better care earlier, reducing stigma and combating discrimination.

However, said Dhaliwal, barriers to progress included stigma and discrimination.

“The involvement of PLWHA is a two way process where they become involved as treatment managers, planners and advocates, not just as recipients.”

The Alliance recommends: “The capacity of PLWHA groups should be strengthened and supported on several levels to address practical issues of improving access to treatment. Increasing the involvement of PLWHA is an important strategy for improving access to treatment and reducing stigma and discrimination.”

The conference heard a similar message from Milly Katana, a Ugandan AIDS activist and HIV positive treatment advocate, who delivered a plenary session address saying communities should take the lead in the movement to increase access to medication.

Katana said communities – which she identified as largely unpaid groups of women, youth and people with HIV – had always taken the lead in responding to the epidemic.

“Communities must engage in the debate and actions about determining how best to access the most competitively priced, high quality drugs in low resource settings, and how to provide treatment to people who are in greatest need,” she said.

She said communities were critical partners in this endeavour and called on scientists and clinicians to consult people with long experience working in the field with little or no funding.

“The world needs more resources to combat HIV/AIDS,” Katana said. “However, we have some resources, which have accumulated over the years, especially human resources and skills, and knowledge of what works and what does not work for prevention. Community groups need to put this to maximum use.”

In Zambia and Botswana, volunteers have been trained to do home visits and outreach, and they can do more, Katana said. “All they need is bicycles in some cases.”

AIDS Empowerment and Treatment International, (AIDSETI) held a press conference to outline a plan to treat 30,000 people in 15 countries in Africa and the Caribbean within two years and to provide diagnostic services to 200,000.

AIDSETI, an umbrella of 23 PLWHA organisations, has applied to the Global Fund for finance. The programme would connect infected individuals with existing PLWHA-led associations already providing medical treatment, including antiretroviral therapy.
Our PLWHA associations have achieved impressive treatment success with their pilot treatment programmes in some of the poorest countries in the world,” said AIDSETI president and CEO Hans Binswanger, a Washington economist.

The AIDSETI programme would teach positive survival skills to 200,000 people, provide diagnostic monitoring services to 200,000 people, provide prophylactic and curative treatment for OIs to 60,000 people, provide ARVs to 50,000 people, combat stigma and engage local associations in the work.

The total budget for the first two years would be $29,097,000. They are seeking $20,430,000 funding from the Global Fund. AIDSETI was launched in 2000 and is run by people infected and affected by HIV. Two thirds of board members are positive, more than half are women and more than half are from the south. The board includes positive doctors like Dr Francoise Ndayishimiye who runs a programme with 1,000 patients in Burundi, and Assana Sangare, the AIDS minister of the Cote d’Ivoire.

Their programme would care for positive people in Burkina Faso, Burundi, Cote d’Ivoire, Cuba, Dominican Republic, Ethiopia, Guinea, Haiti, Jamaica, Kenya, Tanzania, Togo, Trinidad and Tobago, Uganda and Zimbabwe.


Useful link:
http://www.aidseti.org/

ART can successfully tackle advanced disease in resource poor settings, reports MSF

Graham McKerrow, HIV i-Base

Preliminary results of a study of antiretroviral treatment (ART) provided by Médecins Sans Frontières as part of a package of services available at three government-run primary health care centres of a poor South African township, suggest that ART can be successfully used to tackle advanced disease in a resource-poor setting.

Toby Kasper of MSF made a presentation about treatment using Brazilian-made generic ARVs at three dedicated HIV clinics in Khayelitsha, a poor township about 30km from Cape Town.

MSF started the clinics with 3,000 patients in April 2000. They offer triple therapy together with CD4+ T cell and viral load counts. Third line treatment is quadruple therapy.

Patients with advanced disease (CD4+ T cell counts <200, WHO stage 3/4) were eligible for the programme and 180 were enrolled, all with poor health and few with prior ARV experience.

Kasper reported that 88% were still living after nine months. There was no control group “but we are sure there would be many more deaths without therapy”. He said the incidence rates of OIs were 69% less, with TB 85% less, than studies show in non-treated people. He reported substantial increases in CD4 T cell counts and lower viral loads after six months.

Kasper commented: “Recently there have been a number of articles published suggesting that treatment and prevention are diametrically opposed. Our experience in Khayelitsha is precisely the opposite. What we see is treatment promoting prevention and prevention promoting treatment.”

Kasper said the patients, the provincial government, the University of Cape Town and the Treatment Action Campaign were partners in the project and then he explained the process for selecting participants. Doctors made the first selection on the basis of the diagnostic assays. The second phase, to decide which of those eligible would actually receive treatment, was made by community-based groups.

The treatment was provided free to patients together with an adherence support programme, and Kasper added: “MSF believes the government could be doing a lot more to provide ART. There is a lot of health care capacity in South Africa. There is a lot more that could be done than is being done now.”

The authors conclude: “These results support calls to expand access to antiretrovirals in developing countries.”


Investment in treatment and care significantly reduces company health and social expenditure in Abidjan

Graham McKerrow, HIV i-Base

A study comparing the costs of HIV and the costs of treatment and care for employees of a private company in Cote d’Ivoire concludes that investing in the provision of antiretroviral treatment (ART) and care has significantly decreased company expenditure.

SP Eholie presented the findings of a study by colleagues at the Service des Maladies Infectieuses et Tropicales at Abidjan, Cote D’Ivoire. They assessed the impact of HIV and the impact of treatment of employees at a private electricity company at Abidjan with 3,500 employees.

They analysed social impact in the form of absenteeism and employee replacement, and the economic impact in the form of low productivity, cost of care, replacements and funerals over two time periods (1998-1999 vs 1999-2000) before and after the introduction of ARV therapy.

The researchers compared direct and indirect costs of offering care and antiretroviral treatment to HIV positive staff. There were 66 people on treatment. The management team in collaboration with the employees union set up a solidarity fund for ART and the promotion of voluntary HIV counselling and testing.

Eholie reported that the main effects of HIV were absenteeism, employee redeployment to other positions, and social impact in the form of fear and funerals.

The economic effects included low productivity and an increased number of medical consultations and hospitalisations. The average cost of treatment of opportunistic infections was $15,385 per patient. Other costs included $26,154 for solidarity funds and $107,692 for funeral expenses.

Eholie told delegates that sick leave was cut remarkably steeply, from 335 days per month to 22.5, and HIV deaths were down from 16 to nine in the two periods.

Between the two time periods, the costs of caring for positive employees decreased from $338,462 to $153,846, and opportunity costs from $1,539,077 to $61,538.

The researchers conclude: “Company-level strategy including work-based prevention activities, voluntary HIV counselling and testing, and the provision of care and ARVs has significantly decreased the company health and social expenditures.”

Eholie said that the findings advocate comprehensive HIV/AIDS counselling and treatment including ART. He said: “It is better to contribute for life than for death.”

—The Guardian newspaper reported on 7 August that Anglo American has become the first multinational corporation to provide its South African staff with free ART.


Financing the global response to the epidemic will cost $9.2 billion a year, according to one estimate

Graham McKerrow, HIV i-Base

Delegates’ clothes and bags and the conference buildings were littered with little orange stickers demanding “Cheap drugs for all! Where is the $10 billion?” and during the week this figure gained currency as the amount required to respond meaningfully to the epidemic. Two years ago, at Durban, the big issue had been to find the political leadership to tackle the epidemic in developing countries. At Barcelona the big issue was how to pay the costs, so there was a good turnout for a session on Tuesday morning entitled Financing the Global Epidemic.

Various academics have estimated what it would cost to mount an effective response to an epidemic that has resulted in 40 million people living with the virus, and one that is now accepted as being in an early stage of its development.

One is Professor Stefano Bertozzi of the National Institute of Public Health in Mexico and the University of California at San Francisco and he was the first speaker of the session.

Bertozzi estimates it would cost $9.2 billion a year with just over half of that ($4.8 billion) being spent on prevention, and slightly less than half of it ($4.4 billion) being spent on care, which would include antiretroviral treatment for 3.2 million people by 2005.

Bertozzi and colleagues prepared their work for the United Nations General Assembly Special Session on AIDS (UNGASS) in June last year when it was decided to launch the Global Fund to Fight AIDS, TB and Malaria. Other estimates have been
higher and the Global Fund has yet to announce its target, but many speakers and groups at the conference seemed to accept a figure of $10 billion was needed annually. Others said this figure was far too small and up to $25 billion was needed.

A different exercise by the World Health Organisation’s Commission on Macroeconomics and Health estimated that $13.6 billion to $15.4 billion would be needed annually on top of what is already spent if the response to HIV included upgrading infrastructure.

Bertozzi explained that his task had been to estimate the resource needs up to 2005 without significantly extending the health infrastructure: with no new clinics and little extra training.

“These are obviously crystal ball kind of estimates,” Bertozzi admitted, “taking small scale costs rashly scaled up across the globe, but nevertheless they play a role.”

The money would cover the costs of palliative care, treatment for opportunistic infections, blood tests, prophylaxis for OIs and antiretrovirals. It would also pay for prevention initiatives and for the support of orphans.

Bertozzi insisted his estimate would “not take us to where we would like to be” in 2005 but, accepting a country’s existing infrastructure, where it could be in 2005 with extra resources.

And he emphasised: “It does not pretend to be an estimate of the resources needed to care for all people living with HIV/AIDS or to prevent all new infections by 2005.”

Bertozzi said of his estimate: “We couldn’t know how much would be saved with better ARV deals. The model has an idealised view in which the poor pay less than the rich. Our estimate is that poor countries pay less than the current lowest deal, which is for South Africa.

“But negotiating capacity more than need predicts better deals in many parts of the world,” he said.

The Bertozzi model did not take into account how much money might be wasted in inefficiency and corruption. “In the real world it will not be as efficient as we modelled it. In all ways we underestimated the figures,” he said. And he summed up: “The resources needed by 2005 are not there yet but they are more than reasonable, they are needed and they are feasible.”

Dr Crispus Kiyonga, Chair of the Global Fund, and former minister of health in Uganda, said the fund has raised $2.1 billion in promises but only $300 million has been received. They have already approved grants of $616 million over two years.

Hans Binswanger spoke movingly about other ways of financing the response to the epidemic. An economist and advisor to the World Bank, and himself positive, he has launched an organisation called AIDS Empowerment and Treatment International (AIDSETI), a network of 23 national organisations of PLWHA.

He said that 10% of people can afford to pay for their treatment but he asked “Who is going to pay for the 90% unable to pay?”

Binswanger, from Washington, said he was asked last year if he couldn’t save a single life: “Of course I could, on my salary from the World Bank. Then I had the humbling realisation that I was simply not willing to pay.”

So he volunteered to pay for the treatment of an orphan in Uganda. He was given the names of two children, Ronaldo, aged 8, and James, aged 6, and left to choose which would get treatment at his expense. On medical advice he chose Ronaldo.

“Tears came to my eyes for James,” he told the 500 delegates at the session.

Binswanger criticised people for being unwilling to pay and highlighted governments “like those being sued by activists in Brazil and South Africa”, HIV activists in the north, donor governments and pharmaceutical companies.

Then he asked his audience: “What can you do? Become willing to pay – for at least one child, one woman or one man.”

Links:
The Global Fund is at:  http://www.globalfundatm.org/index.html
The Commission on Macroeconomics and Health is at:  http://www.cmhealth.org/
AIDSETI is at:  http://www.aidseti.org/

The Global Fund: what, where, how much?
Graham McKerrow, HIV i-Base

The Global Fund to fight AIDS, TB and Malaria, is barely a year old, is recruiting 50 staff to work at offices based in Geneva, and has already promised $1.6 billion dollars over the next six years for prevention and treatment in the poorest countries in the world.

It has advertised seven senior posts on its website and in the 13 July issue of the Economist magazine, and promises a slim and efficient organisation.
Dr Richard Feachem, a British national, was appointed the first executive director of the Global Fund. He was founding director of the Institute for Global Health in San Francisco, and professor of international health at the University of California, San Francisco and Berkeley. He is also a visiting professor at London University. Previously, he was Dean of the London School of Hygiene and Tropical Medicine.

There have already been demands for Feacham to be sacked after he said in June: “We have got plenty [of money] to start with. The ball is in our court to demonstrate results.” He was criticised for suggesting the fund should “demonstrate results” before undertaking further fundraising.

The Fund’s board includes the heads of several international AIDS programmes, the managing director of McKinsey & Company, and four government ministers including British development secretary Clare Short and US health secretary Tommy Thompson.

Feacham has promised to announce a global plan of action for HIV/AIDS in October. He told the Barcelona conference that it would include the fund’s financial estimates of resources needed and rates of expenditure over the next several years.

Hopes are riding on the effectiveness of this independent public-private organisation to produce unprecedented results. Feacham has promised to be innovative. “We will take risks. We will fail. We will make mistakes. We will learn and we will move ahead,” he said in Washington recently.

The fund has so far committed $1.6 billion to 40 programmes in 31 countries, 60% of this going to HIV/AIDS programmes. $616 billion is committed for the first two years, with the remainder dependent on performance up to then. Feacham told delegates: “These commitments will double the current number of people receiving HAART in the developing world, and in Africa the number of HAART recipients will increase six-fold as a result of these commitments.” He added: “This is nothing like enough.”

Useful link: [http://www.globalfundatm.org/index.html](http://www.globalfundatm.org/index.html)

**Comment**

It is not difficult to wish the Global Fund well. It is good to see it move swiftly to fund projects and to see it make future funding dependent on results. It is also heartening to hear that it promises to be slim and efficient. We will take its word for now that a staff of 50 is really slim. We will also give them the benefit of the doubt that the director needs to receive the same pay as the director of the World Health Organisation and that staff need to get paid at the same levels as do UN employees – notoriously well! Perhaps it shows a commitment to hiring only the best.

But why does the Global Fund have offices in Geneva? Surely it would be cheaper to open offices in a developing country and make sense to spend money where it is needed. It would mean rents, salaries and fancy lunches could help a struggling economy rather than one of the richest in the world. It doesn’t make the Global Fund look like the ground breaking initiative it claims to be. It doesn’t make it look very global.

The critical thing now, though, is for people to pressure rich governments to give more money – every year – to the fund and for the fund to pass it on swiftly to projects in the field. So far the fund has been given $300 million and promised a further $1.8 billion. Even 9.2 billion annually, as estimated by Professor Stefano Bertozzi (see separate story) will only slow the spread of the virus and treat just 3.2 million of the 40 million people with the virus.

It is estimated the England-Brazil clash in the football world cup cost the British economy $2 billion. So, as one speaker at Barcelona said, a $10 billion pot would be the price of five soccer games. Another speaker, Dr Amir Attaran from Harvard, said that in 2000 Britain spent $147 million, more than any other country, on international HIV/AIDS work — about half the production budget of the movie Titanic. We have to persuade governments, and their voters, to think on a different scale.

**Leading businesses spurn Global Fund**

Graham McKerrow, HIV i-Base

Senior executives from some of the biggest corporations in the world told a satellite meeting at Barcelona that they would not contribute a penny to the Global Fund for AIDS, TB and Malaria.

At a satellite meeting held by the Global Business Coalition on HIV/AIDS, representatives from seven major companies
including Hewlett-Packard, DaimlerChrysler and AOL Time Warner answered questions chosen in advance by the Coalition. The first question asked why business hadn’t contributed more to the Global Fund. Karl-Heinz Schlaiss, chief advisor on external affairs for DaimlerChrysler, said it was not the responsibility of businesses: “It is a matter for governments.” Peter Roach, social marketing controller of SSL International, a condom producer, said they donated condoms rather than money. Stuart Burden, director for the Americas, worldwide community affairs at Levi Strauss & Co, said that over several years his company had given more than $25 million to AIDS projects and they preferred to continue with projects they knew rather than give money to a new fund. However, Richard Socarides, vice president of AOL Time Warner Foundation, agreed: “Business should do more.” But he didn’t know how to persuade corporations to donate to the Global Fund. John Hassell, director for federal, state and government affairs at Hewlett-Packard and Gaby Magomola, chairman of the South African Business Coalition on HIV/AIDS, said they didn’t know why more had not been contributed by business. Hassell warned: “If we are held responsible for financing the Global Fund, we will crawl back into the sand.” A member of the audience asked if companies were afraid to associate their brands with AIDS. The company executives said their companies were not afraid but Burden said he had been involved in other AIDS fundraising and one company donated $100,000 on condition their name was not revealed. “Yes, there is stigma,” he said. However, he said his company was pleased to be associated with the cause, explaining: “People would rather buy their jeans from a company with social responsibility. It’s good for business.” Ben Plumley, executive director of the Global Business Coalition, told the meeting that his organisation was “building up our credibility” so that it can influence companies to do more, such as give money or provide antiretroviral treatment to employees. Another member of the audience and employee of DaimlerChrysler in South Africa said: “Looking after staff is part of the job of maximising profits.”

14 Caribbean governments sign cut-price drugs agreement with six pharmaceutical companies

Graham McKerrow, HIV i-Base

The Pan-Caribbean Partnership of 14 nations signed an agreement in Barcelona with six leading pharmaceutical companies for the supply of cut-price drugs – in a move that is likely to set an example for further regional negotiations.

The Caribbean has 500,000 people with HIV and the highest incidence of the virus after southern Africa.

“This agreement is a catalyst for action,” Dr Denzil Douglas, the prime minister of St Kitts and Nevis, told a press conference in Barcelona. “This is an important initiative and is a regional approach to find solutions for small nations.”

He described it as a “framework” agreement without detailed prices but said: “We will shortly be putting together a task force to work with the pharmaceutical companies.”

Douglas said the agreement is to provide treatment for 15,000 people in the first year, another 25,000 in the second year and a further 35,000 in the third year, making a total of 75,000 of the 80,000 who would need treatment.

Dr James St Catherine, programme manager for health sector development at the Caribbean Community (CARICOM), said they expected the companies to supply drugs at about $500 to $800 per patient per year.

“The costs are still too great for some countries like Haiti, Jamaica and Guyana, to name just a few, so we have to work on the possibility of [obtaining] generics,” he said.

Dr Eddie Green, assistant general secretary of CARICOM, said: “Some of the companies have agreed to offer their drugs and diagnostics at the lowest price they offer to the least developed countries of Africa. This is a very significant offer.”

The agreement is with BMS, Hoffmann-La Roche, Boehringer Ingelheim, GlaxoSmithKline, Abbott Laboratories and MSD, but they expect other companies and more countries to join the agreement.

The day before the agreement was signed the health economist Prof Stefano Bertozzi had told the conference that collective negotiation by small groups of poor nations or by regions would be the most efficient way to achieve low drug prices and to avoid corruption.

When the Pan-Caribbean Partnership was established last year Dr Peter Piot of UNAIDS, commented: “An intensified
response requires additional resources. Clearly the need for resources against HIV and AIDS far outstrips their availability. According to the University of the West Indies, a conservative estimate of the cost of a comprehensive response to the epidemic in the Caribbean would be in the order of $260 million a year, ten times more than the current HIV/AIDS-related international spending in the region."

Link:
http://www.caricom.org/

C O M M E N T

The countries and corporations involved in this historic deal are to be congratulated on their framework agreement and they deserve support from the Global Fund, World Bank and bilateral donors to see this agreement produce quick results for the people in the region who need treatment. However, the companies would do well to remember that money is given to provide essential healthcare, not to make multinationals more profitable. With the introduction of special prices and the production of generic drugs the cost of combination treatment is being reduced in some nations to $300 per person per year and some people are now setting a target of cutting that price to $50. If this agreement can match the lowest prices and set an example for other regional agreements, it will benefit people far from the Caribbean as well as those in whose name it is signed.

Thailand offers low-cost transfer to African countries of technology for the local production of generic antiretrovirals

Graham McKerrow, HIV i-Base

The Thai Government Pharmaceutical Organisation (GPO), which manufactures more than 300 types of pharmaceuticals including antiretroviral drugs, announced in Barcelona that it wishes to cooperate with poor countries to facilitate the transfer of the technology necessary for the local production of drugs.

Dr Krisana Kraisintu of the GPO told delegates that his organisation wanted to see a collaboration between Thailand and Africa. He said: “The technology transfer is from government to government, from one developing country to others. The price should be as low as possible so that governments can provide free treatment, or at the lowest possible price.”

Kraisintu said there were three keys to a successful and low cost provision of generic drugs around the world. They were to use generic drugs, to negotiate at the national or regional level, and to produce at the national or regional level.

He emphasised that any technology transfer would have to include advice on quality, quantity and the continuity of supply, as well as TRIPS trade regulations and local drugs licences.

Kraisintu ended his presentation by saying that their goal was to treat three million people within two years.

Generic antiretrovirals are currently produced in Thailand and Brazil under the auspices of the government and in India by the private sector. The World Health Organisation Regional Office for Africa (WHO/AFRO) and Thailand are in dialogue to explore the possibilities for technology transfer.

The paper presented by Kraisintu at a session entitled Towards a Political Economy of Access, recommended: “WHO/AFRO should provide support to countries of interest for the implementation of technology transfer with special emphasis on institutional capacity building and technical assistance at country level.”[1]

A separate presentation by the Thai GPO earlier in the conference said it currently produces zidovudine syrup and capsules, didanosine powder forms, stavudine syrup and capsules, Lamivudine syrup and tablets, zidovudine and Lamivudine tablets, nevirapine tablets, saquinavir capsules and nelfinavir tablets. A combination of stavudine, Lamivudine and nevirapine is also produced. Drugs for opportunistic infections made by the GPO include clarithromycin tablets, fluconazole capsules, itraconazole capsules, amphotericin B injection, lipid emulsion and liposomes.[2]

The abstract for that presentation concluded: “We can now ensure that in Thailand the access to antiretroviral drugs is feasible, affordable and cost effective.”

Brazilian researchers reported that they had developed a mathematical model whereby different income-level countries paid different prices for drugs in a way that provided treatment for those who needed it and protected drug company profits.[3] Researchers at the Fundação Oswaldo Cruz in Rio de Janeiro reported: ”If the high-income countries acquire
the medicine at the price originally stipulated by the drug company and all other countries acquire the medicine at the price of the generic, approximately 70% of the profit of the drug company is maintained.

"Additionally, if the high-income countries pay the original price, the medium and low-income countries pay 25% more than the cost price, and the very poor countries acquire the medicine at the cost price, the profit of the drug company is totally preserved."

They conclude that ARV medicines could be made available to developing countries at viable commercial prices without substantially undermining the drugs company profit. However, acquisition of ARV medicines in the very poor countries will require the assistance of the Global Fund.

References:

Informal market plays a role in distributing antiretrovirals but exposes clients to risks

Graham McKerrow, HIV i-Base

The informal market in antiretrovirals (ARVs) in Chile is poorly documented but is perceived to be growing and exposes clients and vendors to several risks, according to a paper presented by Christian Morales of the Montreal University, Canada, and the Chilean Drugs Access Initiative.

Morales said the informal market takes many forms. One is that individuals go to Spain or Argentina and buy drugs there, some of which they use themselves and some of which they sell to raise money to buy more drugs and so continue the cycle.

The other main way the informal market works is that some people get free drugs but choose to sell them to raise money to buy food; they choose a higher quality of life for a shorter period of time, over a longer poorer-quality life.

The informal market constitutes major public health challenges, reported Morales and colleagues. Clients are exposed to ARVs from doubtful sources, which may be of sub-optimal quality. Discontinuity of supply may cause resistances. Patients don’t receive adequate counselling and are exposed to stress.

Vendors selling their own ARVs undermine their health and may also develop resistances.

Morales told the conference that Chile treats 81% of people who need treatment in a mixed public and private health system. The researchers recommend the universal provision of ARVs.


Virus, damned virus, and statistics: The epidemic in numbers

Graham McKerrow, HIV i-Base

- 40 million people are living with HIV
- 94% of PLWHA are in developing countries
- 3 million died with AIDS in 2001
- 1.7 million died of TB the previous year
- 1 million were killed by malaria that year
- HIV has been recorded in almost every country
- Seven countries in sub-Saharan Africa have HIV prevalence in adults over 20%
- In four of those countries one in three adults has HIV
- Prevalence rates can reach 50% in major cities like Francistown, Gabarone or Mbabane
• GDP has fallen 2.6% in countries where prevalence is more than 20%
• By 2020 more than 25% of the workforce in some countries may be lost to AIDS
• In Kenya AIDS accounts for three out of every four deaths in the police force
• By last year 13.4 million children had lost one or both parents to AIDS
• By 2010 that figure will be 25 million
• Nearly half of all new infections are among people aged 15 to 24
• More than two million young people were infected last year
• In two years, reported annual HIV infections in Russian IDUs aged 10 to 19 rose from 300 to 10,000
• Without comprehensive intervention another 45 million people will have HIV by 2010
• If rich and poor countries keep their promises, 29 million of these infections could be avoided
• Delaying this response by one year will cost five million lives
• $2.1 billion has been promised to the Global Fund to Fight AIDS, TB and Malaria
• Only $300 million has been received by the fund
• $3 billion is needed to respond to TB and malaria alone
• Less than 1% of PLWHA in developing countries can access ART
• 28 million Africans have HIV
• Only 30,000 Africans receive ART
• 230,000 people receive ART in developing countries
• Half of them are in one country: Brazil
• Less than 4% of people who need ART in the developing world can access it
• WHO wants 3 million more people treated by 2005
• Africa faces a shortfall of 2 billion condoms
• The Global Fund has promised $1.6 billion over five years for treatment and prevention of the three diseases
• These Global Fund dollars will double the number of people on ART in developing countries
• These Global Fund dollars will increase six-fold the provision of ARVs in Africa
• There are 200,000 AIDS orphans in Haiti
• 750,000 babies are born with HIV every year
• 30 presidents or deputies have taken direct command of their national AIDS responses

Sources: the World Health Organisation, The Global Fund to Fight AIDS, TB and Malaria, UNAIDS.

CLINICAL SCIENCE

Abacavir hypersensitivity reactions in patients who rechallenge after interruptions for reasons other than hypersensitivity

Paul Blanchard, HIV i-Base

Hypersensitivity reactions to abacavir are known to occur in approximately 5% of patients initiating this drug for the first time. The majority of these reactions tend to occur in the first six weeks of abacavir therapy. Such reactions may be severe, rapidly progressive and occasionally fatal. Life threatening reactions have also been described after rechallenge with abacavir in patients with a previous hypersensitivity reaction.

The risk of hypersensitivity reactions to abacavir in patients who interrupt therapy for reasons other than a previous hypersensitivity reaction is not clearly defined. Guidance, however, is given that patients should not reintroduce abacavir after treatment interruption regardless of the reason for interruption.

Previous studies have identified hypersensitivity reaction in approximately 5% of adult and paediatric patients receiving abacavir. Symptoms usually appear within the first 6 weeks of treatment with abacavir although these reactions may occur at any time during therapy. A letter published in AIDS by Juan Berenguer and colleagues reported on interruption and reintroduction of abacavir in 20 patients with no previous evidence of hypersensitivity to abacavir. A total of 25 interruptions occurred in these 20 patients with a mean duration of interruption of 13 days. After a mean follow-up of 58 days after abacavir reintroduction none of these 20 patients developed clinical manifestations suggestive of rechallenge like reaction to abacavir.

The risk of adverse reactions after restarting abacavir therapy in patients who had discontinued the drug for more than 24 hours for reasons other than hypersensitivity was assessed by Martin and colleagues using an interview based study. Of 190 patients interviewed 52 (27.4%) were found to have interrupted abacavir for more than 24 hours.
Of these 52 patients, four described experiencing reactions after restarting abacavir. Three (5.8%) had mild symptoms and continued abacavir (transient rash, cough, gastric upset and headache) and one (1.9%) experienced a definite hypersensitivity reaction leading to abacavir discontinuation.

This one patient with hypersensitivity reaction had taken abacavir for seven months without any adverse reaction. He discontinued abacavir for personal reasons during three days. After restarting abacavir he experienced cough, pharyngitis, fever and extended cutaneous rash.

The group commented that abacavir nonadherence was frequent in this cohort of patients from a hospital clinic in Barcelona. They concluded, however, that even though this kind of reaction seems to be rare, close monitoring of abacavir reintroduction seems clearly justified in all cases due to the acute onset and the potentially life threatening nature of the hypersensitivity reaction.

References

COMMENTS
Perhaps the greatest problem with monitoring reintroduction is that patients interrupt and restart without informing their clinicians. Further efforts must be made to ensure patients are fully aware of the issues involved in abacavir interruption.

Prolonged CNS side-effects of efavirenz can be severe and lead to treatment discontinuation

Paul Blanchard, HIV i-Base

Side effects attributable to the central nervous system (CNS) effects of efavirenz commonly occur within the first days following initiation of this drug and normally resolve within two to four weeks. These short term side effects have been reported to affect 53 % of patients initiating efavirenz. Some physicians and patients, however, have experienced much longer lasting neuropsychological adverse reactions.

Reynes and colleagues reported the results of their Sensio study which focused on the neuropsychological adverse reactions (NPAR) self-reported by HIV-infected patients being treated with an ARV regimen including efavirenz. Data collection was by questionnaire measuring frequency, severity and outcome of efavirenz related NPAR. Thirty three items were included addressing sleep disturbances, behavioural changes, mood disturbances, anxiety, cognitive disorders, hallucinations, dizziness and general impact on quality of life. All patients administered the questionnaire had received efavirenz for a minimum of three months.

Patients with frequent symptoms before initiation of efavirenz were excluded and only symptoms appearing under treatment with efavirenz focused upon. A total of 199 questionnaires were analysed.

More severe psychiatric disorders were reported in some patients. 10.3% (n=18) reported emergent suicidal ideations after initiation of efavirenz associated with other depressive symptoms. Late onset suicidal ideation occurred in XX% (n=8) and had been long lasting in XX% (n=10). Symptomatic treatment of NPAR was necessary in 10.3% (n=18) usually consisting of benzodiazepines alone or in combination with antidepressants. Overall 6.3% of patients discontinued efavirenz later than three months after initiation due to intolerability of NPAR.

The study investigators concluded that;
Sleep disturbances and dizziness occurred mostly at the beginning of efavirenz therapy
NPAR which persisted or worsened over the three month treatment period were anxiety, behavioural troubles, sadness and cognitive disorders
A high percentage of patients reported suicidal ideations at the time of study whereas none did before efavirenz initiation
NPAR related to efavirenz seriously affects patients quality of life (23.1%) although most patients are able to maintain efavirenz in their regimen.

COMMENTS

It is clear from this study that patients can and will tolerate the adverse effects of efavirenz over many months despite a measurable impact on quality of life. Perhaps both practitioners and patients should be less tolerant, and more ready to switch to acceptable alternatives within a regimen.

Paediatric reports at ICA 2002

Polly Clayden, HIV i-Base

Four drug regimen for infants

Triple drug regimens are insufficiently potent to achieve undetectable viral load in more than 50% of sick infants. Dr Gareth Tudor Williams presented results at a median of 48 weeks (and up to 108 weeks) in an oral abstract from a small cohort of 18 symptomatic infants treated with a four drug, nevirapine –containing regimen [1].

The infants presented with opportunistic infections, including PCP and CMV and had a median baseline viral load of >750,000 copies/ml. They received a regimen of: zidovudine (360 mg/m2/day), lamivudine (8mg/kg/day), abacavir (16mg/kg/day) and nevirapine [NVP] (120 mg/m2/day, then 300mg/m2/day from Day 14 if no rash). This was given BID and the investigators reported that these are ‘…4 palatable suspensions that require no food restrictions.’

Of the group, two children developed NVP associated hepatitis (at weeks 1 and 10) and one child vomited abacavir consistently. Their treatment was changed to lopinavir/r (data excluded). Three children developed NVP associated rash, but continued treatment. There were no cases of abacavir hypersensitivity. 1 child discontinued abacavir at 14 weeks and 1 child stopped zidovudine at week 24, each due to GI intolerance, but continued treatment on 3 drugs (data included).

The 15 children achieved undetectable VL (<400 copies) by a median of 16 weeks, and all were consistently undetectable from week 48 and the median time to reach normal CD4 counts and weight for age was 48 weeks.

The investigators reported that amongst this cohort of infants with advanced disease, ‘15 of 18 children achieved sustained viral suppression and subsequent normalisation of CD4 counts and weight for age on a twice-daily, protease-sparing 4 drug combination.’ Initiating more potent therapy upfront, particularly for children with fairly advanced symptoms may well achieve more satisfactory results than standard triple drug combinations.

Abacavir clearance

Dose finding in children is notoriously difficult to achieve. An oral poster presentation evaluated whether defining abacavir’s (ABC) metabolic profile may offer insights into known differences in dose requirements and pharmacokinetics between children and adults [2]. Additionally the authors speculated that variable metabolite formation could be relevant for patients at risk for ABC hypersensitivity reactions.

ABC systemic clearance (CLabc) is primarily determined by the extent of formation of glucuronide (GLU) and carboxylate (CAR) metabolites.

The pharmacokinetics of ABC, GLU, and CAR were evaluated after administration of a dose of 8 mg/kg of ABC given to HIV infected children stratified by both Tanner stage and gender. Plasma concentrations (n=9) of ABC, GLU, and CAR were determined by HPLC. A pharmacokinetic model for parent and metabolites was fit to each patients data and a metabolite phenotype was defined by ratio of GLU and CAR to ABC.

The investigators reported that abacavir systematic clearance is highly variable (CLabc varied > 5 fold with median (range) of 523 (245-1360) ml/min/m2), and found glucuronidation to be an important determinant. A single blood sample is informative for glucuronidation phenotype and distinguishes among patients with low or high CLABC. CAR metabolite profiles were less informative but further studies may identify subjects with important differences in this metabolic pathway. Genotypic studies in progress will clarify the basis for the phenotypic differences in CLABC. They concluded that ‘ABC glucuronidation phenotype warrants further study to identify patients with high CLABC and patients who experience ABC hypersensitivity reactions.’

Adherence

Adherence has been shown repeatedly to be a strong determinant of treatment success but there are few studies of adherence to highly active antiretroviral therapy (HAART) in children.

In an oral presentation by Dr Di Gibb she reported results from adherence questionnaires completed at 4, 12, 24 and 48 weeks by carers of children participating in the PENTA 5 trial (PENTA 5 was designed to evaluate different dual nucleoside reverse transcriptase inhibitor (NRTI) therapy combinations with and without the protease inhibitor (PI) nelfinavir (NFV)) [3].

The questionnaires included questions about the number of doses missed in previous 7 days, about difficulties taking
individual drugs, which doses were hard to remember and how HAART interfered with everyday life. 266 questionnaires were returned, at least one for 108 (84%) of children participating in the trial.

NFV was reported to be the most difficult drug to take – reported in 38% of questionnaires, but this decreased over time, p=0.02. Difficulties in taking and remembering drugs reported were related to fear of disclosure and to unpleasant characteristics of the drugs – taste or smell of tablets or liquid and pill size.

Full adherence was reported in 74% of questionnaires which did not change over time, and was reported more frequently in older children (>10 years) and those with symptomatic HIV. More children reporting full adherence achieved HIV RNA <400 copies/ml - at 24 weeks 75%/48 weeks 79% vs 50%/50% of children reported to be not fully adherent: overall p=0.01). These results are similar to those reported in adults.

The authors concluded that ‘Relatively high adherence levels were reported and were significantly associated with virological response. Social factors were important in explaining non adherence. Further research including randomised studies are required to evaluate ways of improving adherence in HIV infected children.’

Carnitine deficiency and HAART

Carnitine deficiency appears to be associated with antiretroviral use particularly zidovudine (ZDV), unlike adults there are few data reporting on carnitine status in children. A poster from Dr Claudia Fortuny and colleagues looked at possible carnitine deficiency in children and tried to find a relationship between serum carnitine, it’s amino acid precursors, nutritional status and antiretroviral therapy [4].

79 HIV-positive children were monitored. Reference values were established in this pediatric population by measurement of carnitine profile (N=31) and amino acids (N=88) in apparently healthy children who underwent pre-operative laboratory tests for minor surgery.

The investigators reported that serum free and total carnitine, acylcarnitines, methionine and lysine were significantly lower in HIV-positive children compared with the reference values for similar ages (p<0.0001 and carnitine deficiency was observed in 37% of HIV-positive children. No relationship was observed between serum carnitine and severity of symptoms, immunological or nutritional status or lipodystrophy. Free and total carnitine were significantly lower (p=0.002 and p=0.033, respectively) in HIV-infected patients on protease inhibitors (N=56) compared with those on other treatments (N= 23). 80% of HIV-infected children with carnitine deficiency were on protease inhibitors therapy.

They concluded that ‘Carnitine deficiency is frequent in HIV-infected children. Malabsorption or defective synthesis may account for the carnitine deficiency detected in these patients.’ And also noted that ‘The identification of the causes of carnitine deficiency in HIV-infected children are complex. And most probably a combination of multiple factors are involved. Additionally ‘Carnitine measurement seems advisable in HIV-infected children so as to be able to normalize decreased serum and probably tissue levels.’

Treatment interruptions and CD4 decline

Adult data reports a median CD4 decline of approximately 20 cells per month during a structured treatment interruption (STI) [5]. An analysis from the Collaborative HIV Paediatric Surveillance (CHIPS) study evaluated CD4 decline in HIV-positive children stopping HAART therapy for at least one month, after at least 3 months before stopping. CHIPS is a cohort of HIV positive children from 14 centres in UK and Ireland under follow-up from 1996. The investigators emphasized that these were unstructured treatment interruptions.

Data on clinical events, T cell subsets, HIV RNA viral load and ART history were collected on HIV-infected children from 14 centres in the UK and Ireland participating in the CHIPS study (n=43) and 3 children from Rotterdam.

The slope of decline of CD4 cell count and CD4% per month off HAART, adjusting for age, was calculated and compared to changes within the 6 months preceding interruption.

The most common reasons for interruption were ‘request of parents’ (n=10) and poor adherence (n=7). The same HAART was restarted after 11 interruptions, was changed after 18, and 8 children remained off HAART. CD4 count and CD4% were stable prior to interruption and only 11 children had HIV RNA <10,000 copies/ml (of whom 3 <400 copies/ml). Only 6 children were fully suppressed before stopping. During 22 interruptions with sufficient data, average CD4 decline was 18 cells/mm3/month – a median fall similar to that of adults.

The authors concluded that ‘CD4 cell decline rate varied considerably following interruption of HAART in this group of children with high viral load before interruption (possibly implying poor adherence). An approach to paediatric STI trials may be to base the length of STI on the rate of CD4 decline rather than having fixed STI periods.’

CD4 and HIV RNA response following HAART

Another CHIPS evaluation looked at predictors of CD4% and HIV RNA change 6 months after initiation of HAART (taking 3 or more drugs with at least a PI, NNRTI or ABC) [6]. Adult data has suggested that CD4 response to HAART may be relatively
independent of HIV RNA or CD4 count at HAART initiation. This has been poorly evaluated in children. In this study the investigators aimed to describe predictors of response to HAART in children in clinical practice.

HAART was defined as a regimen containing 3 or more drugs of >=2 classes or ABC. Of 627 children 178 were drug naïve at initiation of HAART and had CD4 and HIV-1 RNA values up to 6 months before and 6 months after HAART initiation. The median age was 4.1 years, median CD4% was 16% (CD4 z-score 3.4) and median HIV-1 RNA was 5.3 log10 copies/ml.

Of the regimens used 51% were PI-containing, 39% NNRTI-containing, 19% PI and NNRTI and 8% ABC. NFV was the most commonly used PI and NVP the most common NNRTI.

At 6 months after initiation of therapy 154 (87%) children had higher CD4 than baseline. There was a median increase of 9% CD4 and a median decrease of HIV-1 RNA of 2.6 log. 102 (57%) children were <400 copies.

Adjusting for confounders CD4 rise >10% was inversely correlated with baseline CD4 and age at initiation of HAART. There were no significant additional effects of AIDS status or HIV RNA at start of HAART, calendar year of starting HAART or type of HAART, on CD4 or RNA response. The investigators noted that higher odds may be associated with 4-drug regimens but the number of children taking these was small (n=9).

The investigators concluded that children respond well to HAART irrespective of baseline HIV RNA or clinical status. Adherence may be poorer in younger and asymptomatic children with higher CD4%, whereas older children may be less able to reconstitute their immune system.

Lactic acidosis in newborns

Over recent years in the industrialised world strategies to reduce mother to child transmission (MTCT) have virtually eliminated this mode of transmission. There is however concern that foetal exposure to nucleoside analogues may cause lactic acidosis in some newborn infants.

A poster from Noguera and colleagues clinical symptoms of mitochondrial dysfunction were analysed in a group of 78 children (40 girls and 38 boys) born to HIV-infected women during 24 months (January 2000 - September 2001) [7]. None of the children were HIV positive.

Most of the mothers had received zidovudine (ZDV) in different regimens during pregnancy, 17 mothers received therapies without ZDV and 4 mothers were untreated. Most of the women also received ZDV alone or combined with other antiretrovirals during labour; five mothers received no treatment. All newborns were treated with ZDV. Hyperlactatemia with hyperalaninemia was detected in 39 (50%) children, accompanied with mild acidosis in three cases. Only 3 infants have shown axial hypotonia with a slight delay in psychomotor development. These symptoms did not persist in all cases by the age of six months. In 18 patients, lactate plasma levels have progressed spontaneously to normality within the first six months of life.

The authors concluded that ‘Half of the children exposed in utero or in the neonatal period to NRTIs develop hyperlactatemia, normally benign and self-limited.’ And recommended that ‘A close follow-up of these children is required.’

Metabolic changes

A number of posters looked at lipodystrophy, bone disorders and metabolic changes in children and one poster evaluated the use of bone ultrasound to evaluate bone strength in children.

Dr Brambilla and colleagues evaluated the correlation between metabolic abnormalities, fat mass and visceral adiposity in HAART-treated HIV-positive children [8]. They assessed a group of 37 receiving d4T/3TC+PI, between the ages of 6 and 18 (mean age 12.2 yrs) of which 8 had and 29 had no clinical signs of lipodystrophy. The children were assessed for: 1 lipids, glucose, insulin levels; 2 fat content and distribution (by DXA); 3 visceral fat content (by lumbar MRI). As a group the children had an excellent suppression rate - 35/37 HIV-RNA<50 copies/ml.

The investigators reported hypertriglyceridemia present in 19 (51%), hypercholesterolemia in 19 (51%), elevated LDL cholesterol in 7 (19%), elevated insulin levels in 5 (18%). Triglycerides and insulin levels were more elevated in children exhibiting clinical signs of lipodystrophy than in those without (p<0.009 and p=0.01 respectively). Children with clinical signs of lipodystrophy had higher trunk fat (5.7 ± 2.4 vs 3.7 ± 2.3 kg, p=0.04) and higher visceral fat [86 (34) vs 31 (16) cm2, p= 0.0001], but similar total body fat percent [22 (6) vs 17 (8), p=0.08] when compared to those without. They also found insulin levels were significantly correlated with total body fat (p=0.0009) and with trunk fat (p=0.0006) in all cases; only children with signs of lipodystrophy showed a significant correlation between visceral fat and insulin.

They concluded that ‘HAART treated children show frequent metabolic abnormalities. Fat mass is the best predictor for hyperinsulinism and insulin resistance. Visceral fat, very high in children with clinical signs of lipodystrophy seems to be the major determinant for impaired insulin metabolism.’

Another poster from the same group reported by Alessandra Vigano and colleagues assessed whether progressive harmful changes in body composition are associated with increased exposure to highly active antiretroviral therapy in HIV-infected children [9].
Risk of clinically assessed lipodystrophy appears to increase with the duration of exposure to HAART in HIV-infected adults. This study aimed to assess longitudinal body composition in HIV-positive children receiving HAART using DXA and magnetic resonance imaging (MRI) to estimate regional body composition and visceral fat content (VF).

Thirty seven children as described above were enrolled in the study. DXA scans were performed in all of them at study entry and after 12 months. MRI scans were performed in 14/37 at study entry and after 12 months.

At study entry and at 12 months follow-up mean HAART exposure was 39.3 (4.1) and 50.9 (6.7) months, number of children with clinical signs of lipodystrophy increased from 6 to 8, whereas mean body mass index CD4% and % of children with HIV RNA<50 copies/ml (100 vs 97) and diet remained unchanged. DXAs showed that: Lean mass increased in all HIV positive children according to physiological growth pattern for age; Fat mass did not change significantly and consequently fat % decreased significantly (p=0.04); Fat distribution changed showing a significant increase at trunk level (p=0.006) with a slight decrease in arms; therefore limbs/trunk fat ratio was significantly reduced (p=0.0001) as well as arms fat/lean ratio (p=0.0003). All changes were observed independently from clinical signs of lipodystrophy. In children with lipodystrophy, increase in trunk fat was more pronounced. MRI scans showed an increase in VF in HIV+ with as well as in HIV- without lipodystrophy.

The investigators reported that abnormal fat mass deposition occurs frequently and are a progressive phenomenon in HIV-infected children receiving HAART. They conclude that ‘The prevention as well as an effective and safe treatment of such adverse events need to be urgently considered’ and that ‘These changes of body composition expose children to a high risk for severe psychological repercussions and metabolic abnormalities.’

In a poster presentation Jim Oleske’s group analysed bone disorders in HIV-infected and -exposed children using data from PACTG 219 (this is a long-term study, since 1991, to examine outcomes in 2,695 HIV-positive children and 1,352 HIV negative children exposed to HIV and antiretroviral drugs) [10]. The database was examined for reports of osteopenia, osteonecrosis and any other bone disorders. 38 HIV-positive children were diagnosed with bone disorders.

Fractures were the most common diagnosis, seen in 33 (30 infected, 3 uninfected)/82 (40%), 39% of whom had comorbid conditions such as growth or developmental delay. Three children had rickets (2 infected, 1 uninfected). The 2 HIV infected children with rickets had comorbid malabsorption syndromes. The following conditions were only reported in infected children: osteomyelitis, osteonecrosis and osteopenia. Osteomyelitis was reported in 22 children, 9 female and 13 male, 8 of whom had comorbid conditions. Osteonecrosis was reported in 7 children, 5 male, 2 female involving the hip in 6 and the humerus in 1. Osteopenia was reported in 4 children, 1 girl and 3 boys: 2 had bone fractures as well, and 3 had extensive comorbid conditions, including congenital toxoplasmosis, active CMV, and renal disease.

The investigators found that bone disorders were seen in 2.9% of infected children followed in PACTG 219 as opposed to 0.07% HIV-exposed but uninfected children. They recommend that ‘HIV-infected children need to be monitored for bone disorders in order to determine the role of disease or adverse treatment effects on bone health’.


This relationship had not been previously assessed using objective criteria for lipodystrophy and longitudinal measurements of bone. The study objective was to compare accrual of total body bone mineral content (TBBMC) in HIV positive children using antiretrovirals with and without lipodystrophy (LD).

They found that eight children (29%) were classified as LD+. The mean unadjusted TBBMC was lower in LD+ children at both visits 1 and 2 but these differences were not significant. No significant differences in bone mineral accrual from visit 1 to visit 2 were observed. At both visits, the mean unadjusted total bone density (TBD) was lower in LD+ versus LD- children but the differences were not significant. The differences in log TBBMC and log TBD remained insignificant after adjusting for age, sex, race, height, and weight.

The investigators found that ‘TBBMC accrual does not differ in HIV+children with and without LD. Using objective measurements and criteria are necessary to determine the relationships between LD and bone abnormalities and associated risk factors’.

Finally a poster from Drs Desai and Mathur performed an assessment of bone strength in children with HIV on HAART using a novel non-invasive bone ultrasound

Bone density is generally studied using complicated procedures such as DXA or indirectly assessed using hormone levels. The authors presented the use of a novel Quantitative ultrasound (US) as a simple, non-invasive method of assessing bone strength.

58 children age 3-17 years had bone ultrasounds performed. 38/58 (65.5%) had bone density below the 50th percentile, 26 (45%) below the 25th, 18 (31%) below the 10th percentile and 12 (21%) below the 5th percentile. 29 patients are on one & 18 on two protease inhibitors and 11 on no PI. There was no correlation between bone strength & HIV viral load, CD4 count or PI therapy. Patient & family acceptance of bone US was high. Nutritional counseling was reinforced based on US results.
They concluded ‘Decreased bone strength is common in children on HAART, with a significant percentage having bone strength below the 10th percentile for age and sex. Bone ultrasound is a reliable, non-invasive & easily performed bedside test of bone strength and should be incorporated in the routine assessment of patients on HAART.’

References:

All references from the Program and Abstracts XIV International AIDS Conference Barcelona 2002.
5. Leclerix V, Duong T, McGee L et al. Treatment interruptions of HAART in paediatric HIV: effect on CD4 count. Abstract TuPeB4630
9. Vigano A, Mora S, Beccio S et al. Progressive harmful changes in body composition are associated with increased exposure to highly active antiretroviral therapy in HIV-infected children. Abstract TuPeB4647

Study of MTCT programme finds resistance in women on two doses of monotherapy

Polly Clayden, HIV i-Base

At this conference around fifty lectures, poster presentations and posters addressed the subject of mother to child transmission (MTCT) in resource-poor settings. Of these, however, only two presented programmes to reduce the chances of these children losing their mothers before they even learn to walk.

3-fold increase in resistance with 2 NVP monotherapy doses

Of the many studies using nevirapine monotherapy to reduce MTCT, the most alarming findings were reported in a late breaker poster from John Sullivan [1]. In this study resistance was determined in a group of women receiving two doses of nevirapine – the second dose to offer additional prophylaxis during breastfeeding - compared to a group receiving ZDV/3TC (for seven days).

Genotyping at four to six weeks postpartum detected resistance in 74/111 (67%) of the women receiving nevirapine – largely the K103N and Y181C mutations (62% and 45% respectively). Additionally of the 40/111 HIV-positive infants born to women receiving nevirapine, 21 (53%) had detectable nevirapine resistance mutations at four to six weeks of age. Evaluation of paired mother and infant data suggested that in some cases nevirapine resistant virus could have been transmitted by breastfeeding. No detectable resistance was observed in the 37 women receiving the ZVD/3TC.

Dr Sullivan concluded that as this two maternal dose nevirapine regimen conferred a three-fold increase in selection frequency compared to a single maternal dose – as reported in HIVNET 012 [2] - he recommended that ‘These results favour the use of single dose nevirapine or the seven-day ZDV/3TC regimens for the prevention (note: A more accurate description would be ‘reduction’ given the transmission rate) of MTCT.’

Transmission rates in advanced disease

Further data was presented from the HIVNET 012 trial looking at transmission rates stratified by CD4 and viral load [3]. At the lowest CD4 counts (<=200) at 18 months transmission rates for women receiving nevirapine were 31.6% (vs. 54.9% for ZDV). The investigators concluded that ‘These data support the efficacy of the simple NVP two dose peripartum regimen including women with the most advanced HIV disease.’ No data to evaluate selection of resistance or maternal health in the women receiving these interventions were presented with these findings.

And the good news...

A protocol design from the WHO to be implemented beginning later this year was presented as a poster [4]. The objective of this study is to assess the acceptability, safety and efficacy of HAART (ZDV, 3TC, NVP) to reduce MTCT during pregnancy and to maintain the mothers’ own health. The women participating in the study will be stratified into three groups by CD4 count:

1. CD4 counts below 200 cells/mm3 or AIDS symptoms: all women will be provided with HAART through pregnancy, delivery,
the breastfeeding period and beyond, as they require antiretroviral therapy for the management of their own HIV disease

(2) CD4 counts in the range 200 – 500 cells/mm3: randomisation to either short-course ZDV prophylaxis, or HAART for up to six months post-partum provided that mothers continue to breastfeed

(3) CD4 counts above 500 cells/mm3: ZDV short-course prophylactic regimen

Additionally, all women will receive infant feeding counselling according to WHO recommendations. Women and their infants will be followed for two years post delivery. It is important to note that ZDV+3TC+NVP combination for six months currently costs ~200 USD, similar to infant formula. HAART and treatment of OIs will be provided to all study volunteers with AIDS and to those that develop AIDS during the study. HAART will also be provided to women’s partners and children who require treatment. First results from this protocol will be presented in 2004.

Finally the headline grabbing new programme MTCT-Plus attracted much attention at this conference and was described in an oral presentation by Dr Wafaa El Sadr [5]. This initiative is led by Allan Rosenfield, dean of the Mailman School of Public Health, who asked in Durban ‘Where’s the M in MTCT?’ in a pithy keynote session that began by questioning the ethics of ‘…preventative therapy [that] uses the woman’s body to confer treatment to the child but gives no benefit to the woman’. MTCT-Plus, a joint venture between the Mailman and a coalition of private foundations, acknowledges that, although programmes for the reduction of MTCT have expanded in resource-poor settings, primarily through the use of nevirapine, the women receive nothing for their own or their families’ diseases. They explained that, ‘…this has resulted in an ethical dilemma, inconceivable suffering with millions of orphans struggling to survive without their mothers’.

The programme will expand on existing MTCT sites - including those administered by UNICEF, Médecins Sans Frontières and the WHO - with the establishment of 10-12 MTCT Plus sites in the first phase. It will provide sites with the resources for building multidisciplinary care teams, antiretrovirals, diagnostics and treatment for OIs, thus facilitating a transition from antenatal to ongoing family care. In addition the programme will offer comprehensive patient education and adherence support.

The clinical protocols for this initiative are being finalised and the project is expected to be operational as soon as possible and will be a $100 million dollar plus initiative over the next five years.

With such exciting news on the horizon the only worry is, going back to Dr Rosenfield’s own concerns raised in Durban, that following interventions such as those described earlier ‘…we may be increasing viral resistance to treatment. One thing we don’t want to do with MTCT is make the woman’s condition worse while reducing transmission’ so that a woman could already be disadvantaged due to her treatment history before she even begins MTCT-Plus. What we would like to see are, as Dr El Sadaa described ‘…not only healthy children but mothers that can watch their children grow’.

References

Link: http://www.columbia.edu/cu/news/02/07/mailman_mtc+aids.html

Emergence of resistance in children treated with ddI/ddT after treatment to reduce MTCT

Polly Clayden, HIV i-Base

The main obstacle to using short course and single dose antiretrovirals as an intervention to reduce MTCT is the development of resistance not only for the mothers but also for the infected infants. One study, first presented in Durban, looked at different nucleoside regimens from the most frequently used drugs used in MTCT programmes [1]. In this trial, women were
randomised to four arms and received d4T; ddI; d4T plus ddI and ZDV from 34/36 weeks of gestation until delivery. In addition infants received the same drugs as their mothers within 36 hours of birth and continuing for a six weeks, and infants received off study ddI plus d4T after the six week study period.

A poster presented in Barcelona looked at resistance data from 22 infected infants from this study, that showed no evidence of resistance mutations associated with any of the drugs used at of six-12 weeks of age [2]. One of the infants had the A98G mutation, which is associated with low level nevirapine resistance. This mutation was also evident in the child’s mother who did not report having ever received nevirapine, so is therefore likely to be a naturally occurring polymorphism of HIV-1 subtype C viruses.

Samples were available for 12/22 of the infants at nine-18 months who had received off ddI and d4T study. Of this group six infants had evidence of resistance - five had the rarely reported T69N mutation conferring low-level resistance to ddI and potential low-level resistance to d4T. Two had the Q151M mutation associated with multi-nucleoside resistance and one had the V75I, F77L and F116Y mutations associated with multi-nucleoside resistance.

The investigators concluded that 'These data indicate that HIV-1 infection in infants is not due to the transmission of drug resistant virus following short-course therapy with ddI, d4T and AZT. However continued therapy with ddI plus d4T was associated with resistance in half of the infants.'

References

Correlates of fatigue in HIV disease
Simon Collins, HIV i-Base

Management of fatigue is complicated because it is both a side effect of ARV therapy as well as an underlying symptom associated with HIV disease. It is widely reported outside of HIV care by 90% patients visiting GPs and therefore also easily dismissed as a factor that patients have to learn to live with.

Rarely researched, it is therefore worth reporting results from a small study by K Phillips from University of South Carolina which looked at how often variance in fatigue could be explained by anaemia, or by other factors including sleep quality, daytime sleepiness, anxiety, depression and stress.

Correlates of fatigue were examined in a sample (n=57) of individuals from a community clinic (84% single; 89% African-American; 60% female, with mean age of 31). The mean fatigue score of the group was 4.0, one third of whom were found to be anaemic.

The abstract reported relationships between the study variables using Pearson’s r between fatigue and sleep quality (r = 0.50), depression (r = 0.67), trait anxiety (r = 0.56), state anxiety (r = 0.70), and stress (r = 0.75); all highly significant with a p value = 0.0001. Subsequently, these variables were entered into a back stepwise selection model. Sleep quality and perceived stress were the only variables left in the final model that explained 61% of the variance in fatigue.

The study concluded that while anaemia needs to be corrected when identified in HIV-infected individuals, other factors might significantly contribute to fatigue. Sleep quality and stress need to be addressed by clinicians when treating individuals suffering from fatigue.


Optimum hydroxyurea dose determined
Simon Collins, HIV i-Base

Use of hydroxyurea seems to have reduced over the last two years despite promise when used in salvage therapy to enhance phosphorylation to thymidine (d4T) or cytidine (3TC) analogues, and to potentiate ddI activity and possibly compensate for ddI resistance by re-establishing the nucleotide ratio in favour of ddI. Of note, hydroxyurea is included in both the Montaner and Katlama multiple drug rescue protocols using > 7 drug regimens, and is likely to still remain an important option in multiply drug experienced patients.
In practice, in these and other studies, ddI has been dosed at 500mg BID (twice daily) and toxicity (neutropenia, nausea, skin and nail discoloration, hair-loss and mouth ulcers together with increased risk of ddI side effects of neuropathy and pancreatitis) at this dose has also limited its use in clinical practice.

Franco Lori has led much of the research into HU, including as an ARV adjunct with ddI in reduced ARV combinations and as an immune modulator with treatment interruptions. Lori presented results from the RIGHT 702 study, which randomised 115 HIV-positive patients in a 3x3 factorial design to 600mg, 800-900mg and 1200mg in once, twice or three-times daily dosing, together with d4T/ddI background therapy.

The abstract reports that pairwise comparisons between the 600mg and 800-900mg daily dosing were statistically significant in favour of the 600mg arms at all dosing regimens for proportion of patients < 400 and < 50 copies/ml at both 24 and 48 weeks, although the actual percentages were not reported. BID dosing was reported as superior to QD dosing for virological but not immunological endpoints.

The most effective daily dose for the primary endpoint (% BLQ < 400 copies/ml at week 24) was the 300mg BID arms (p=0.017). The seriousness of higher doses, and the use of hydroxyurea with ddI in general was highlighted by a fatal case of pancreatitis in the 1200mg QD arm – clearly the wrong study for this patient. The practical use of HU is likely to remain in a salvage setting, when other options are limited, supported by close monitoring.


Management of treatment experienced patients

Simon Collins, HIV i-Base

It is difficult to know the number of patients in the UK who are currently on a virologically failing treatment with resistance to three drug classes. Low enrolment in the Optima trial comparing use of Mega-HAART >4 drugs to standard four-drug therapy, with or without a treatment interruption, has been reported to be due to a small pool of patients in this situation, perhaps due to the recent availability of lopinavir/ritonavir.

Nevertheless the numbers are likely to continue to grow before the next ‘best hope’ drugs for resistance virus become widely available. Tipranavir, a protease inhibitor from Boehringer with activity against current PI resistance, likely to be boosted by ritonavir, will not be available in expanded access until late 2003. The first fusion inhibitor, T-20 (enfuvirtide) from Roche/Trimeris, will not be affected by resistance to current agents but will also not become more widely available again until mid 2003 at the earliest. To be effective both these drugs need to be supported by other active drugs within a regimen.

Very encouraging results were presented in Barcelona on both these drugs for salvage therapy.

Although other long promised therapies are now in the early pipeline including integrase inhibitors and other entry inhibitors, the development process, although compressed for HIV, will never be fast enough for those dependent on access to these drugs. Also, access to these compounds within studies may be less likely to offer best treatment for those study participants unless other investigational agents are allowed.

Until these new drugs become available, it is essential to understand several principles in order to optimise individual patient care:

i) accurately targeting active drugs to susceptible virus is the only mechanism for reducing and maintaining a reduced viral load;

ii) resistance is nearly always a sliding scale rather than an on-off process. Therefore some drugs may continue to provide benefit despite low level resistance and some resistance and may therefore be overcome given higher drug pressure.

Both these point to the importance of individualising treatment and individualising dosing through the use of therapeutic drug monitoring.

iii) thirdly, drug resistance appears to result in less replicatively competent virus – and several studies reported on way to understand and exploit this resistance in a salvage setting.

Montaner overview favours Mega-HAART

Options in salvage therapy were supported in an important overview by Julio Montaner. [1] In practice, even with the use of new agents, he suggested that there are essentially only a few strategies:

i) to change to a multiple drug combination – in the hope that a heterogeneous viral resistance population will be affected by multiple different drugs.
ii) to use a period without treatment - to partially revert to wild type virus and the subsequent multiple drug regimen will have higher success.

Results from Barcelona supported both approaches in different degrees, and a third option:

iii) to do nothing and monitor, (Deeks et al) has been shown to hold some patients who are using protease-based combinations clinically stable for up to two years. This is generally recognised as a limited measure because resistance is likely to continue to develop.

Without clear results from large studies, a highly individualised approach to each patient is essential. This takes time and involves a closer standard of care. Many additional common sense aspects of individualising treatment are only possible by using supportive technology such as therapeutic drug monitoring, resistance tests together with expert interpretation and adherence support.

Montaner also introduced the importance of the ‘virtual virus’ as the cumulative sum of worst resistance profile of an individual over time. This requires longitudinal resistance testing, timing of tests (ie when on-treatment) and a full treatment history. Even without baseline resistance tests, if a treatment history implies earlier resistance, then it is important to remember this when reading resistance test results from current treatment. A drug that shows sensitivity on a resistance test is not the same as a drug that is going to be active in any given situation. Resistance tests are only able to indicate resistance to drugs that a patient is using when the sample was taken. Even then, they only provide guidelines for subsequent treatment, and are dependent on sensitive drugs being available.

Montaner’s results using mega-HAART, supported by drug level monitoring with up to nine drugs (median 6, IQR 5-7) in a cohort of 248 multiply drug resistant patients, saw 69% on ITT analysis achieve viral load <400 copies/ml on at least two consecutive counts and 35-40% reach <50 copies/ml at week 48. [2] He also reported that this response is sustained out to 24 months in 80% of his patients who achieve undetectable viral load, and that aiming for this goal in a treatment experienced group is both realistic and sustainable. Even more optimistically he showed that this aggressive response to multiply drug resistant patients produced a Kaplan-Meyer survival response similar to treatment naïve patients.

IQ and Virtual IQ
Numerous previous studies have shown that higher drug levels, especially of PIs, result in greater antiviral activity, and often sufficiently to overcome partial resistance and often shown in studies utilising the virtual IQ. Resistance is rarely an ‘on-off’ switch. The inhibitory quotient (IQ) is essentially the relationship of drug exposure to drug susceptibility of a particular pathogen.

Casado and colleagues from Ramon y Cajal Hospital, Madrid, found significant differences in response depending on whether IQ was > 1 in a prospective study of 51 PI-experienced patients using either indinavir/ritonavir or nelfinavir/saquinavir combinations. Virological response in patients who achieved IQ>1 rather than <1 was –1.68 vs –0.51 log (p=0.04) for nelfinavir; -1.1 vs -0.92 (p=0.03) for saquinavir, and -1.2 vs -0.83 log (p=0.09) for indinavir [3].

Many of the presentations at Barcelona again highlighted the importance of TDM to manage drug interactions used in salvage therapy.

Giga-HAART and drug levels
Two posters from the French Giga-HAART study looked at treatment interruption and drug levels together with multiple drug regimens. Although first presented in Athens last year, and notably not accepted for the Retrovirus conference in February, these results are sufficiently important to report again.

70 patients resistant to three classes of drugs were randomised to either change immediately to a new regimen containing upwards of eight drugs (immediate treatment arm) or to take an eight-week break from treatment before a similar regimen (deferred treatment arm). Giga-HAART regimens were constructed using 3-4 NRTIs + one NNRTI + hydroxyurea + ritonavir (400mg BID) + amprenavir (600mg BID) + another PI (either indinavir 400mg BID or saquinavir 600mg BID or nelfinavir 1250mg BID). This was an advanced population with median baseline viral load and CD4 of 5.3 logs and 27 cells/mm3 respectively. ARV treatment had been used for a mean 6.6 years with exposure to 11 ARV drugs.

An analysis of 63 patients at weeks 12/20 showed a highly significant difference in response between patients who interrupted therapy compared to those who used continuous treatment and these results were sufficient to require the study to close early. [4]

Further analysis of the role of adequate drug levels in the Giga-HAART study (above or below the recommended Cmin) a change in viral load of +0.4 log was common in patients from either arm who were found not to be achieving optimal drug levels. Patients with an adequate Cmin in the immediate treatment arm achieved a viral load reduction of –0.4 logs. In the deferred treatment arm, patients with adequate Cmin levels achieved decreases of –2.0 and –2.6 logs depending on whether they had experienced a shift to wild-type virus during the period off treatment. Patients in the deferred arm with low Cmin levels only achieved reductions of –0.7 logs. [5] As with other studies, sub-optimal drug levels in this study were clearly associated with
minimal comparable responses.

**Viral load responses by drug level:**

<table>
<thead>
<tr>
<th>Immediate arm</th>
<th>Deferred arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate Cmin</td>
<td>- 0.4</td>
</tr>
<tr>
<td>Sub-optimal drug level</td>
<td>+ 0.4</td>
</tr>
</tbody>
</table>

*Cmin levels used in Giga-HAART Study:*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cmin level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>≥ 1100ng/ml</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>≥ 4000ng/ml</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>≥ 2100 ng/ml</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>≥ 1000 ng/ml</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>≥ 3000 ng/ml</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>≥ 250 ng/ml</td>
</tr>
<tr>
<td>Indinavir</td>
<td>≥ 150 ng/ml</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>≥ 1000 ng/ml</td>
</tr>
</tbody>
</table>

**Sequential monotherapy in salvage?**

While Barcelona provided practical support for most of the approaches to salvage therapy that have already been reported in HTB over the last two years, and which are already the basis of the i-Base ‘Guide to Second-line and Salvage Therapy’, there was very little that was new for salvage therapy.

A few days earlier, at the XIth resistance workshop in Seville, a paper from Andrew Phillips from the Royal Free Centre for HIV Medicine, London, suggested a basis for the most radical theoretical approach to salvage therapy discussed this summer. [6]

Phillips suggested that the reduced replicative capacity for most drug resistant virus - all except some NNRTI-associated mutations seem markedly less fit in the presence of drug compared to wild type – may be sufficient to protect CD4 depletion.

Using a previously described model allowing for 128 subpopulations of short-lived cells and resistant combinations of seven ARVs, he calculated that sequential daily (or weekly) monotherapy was as likely to produce sustained 3 log viral suppression over three years as a continuous seven-drug combination. According to the model, under some circumstances, dual or triple therapy may be more likely to work than monotherapy, and it would probably be best to start with double or triple combinations. The only advantages of monotherapy are reduced toxicity and cost.

Importantly, this model worked even in a ‘worst case’ scenario when all 128 resistant subpopulations are present. Although viral resistance would be present on each day of treatment, with effective replicative ratio >1, with whichever drug is being used, the sequential regimen would remain effective because this subpopulation does not have time to grow sufficiently during the short period during which the drug is being taken. The model allows there to be different amounts of each of the 128 different types of virus at any one time. It would also work if 100% of virus is resistant, so long as that virus is sufficiently impaired as a result of those resistance mutations.

This approach is not currently being followed in practice, and one caution is that it may require more classes of resistant drugs than are currently available. However, if the rationale is plausible, this is a study that would work best for people who have already developed strongest resistance, who arguably have few other options, and who would therefore be most likely to want to try this option as they have already developed extensive resistance.

Several other studies at the Seville meeting looked at defining and harnessing reduced viral fitness for clinical benefit and proof of concept case studies will be followed with interest.

*See separate reports in this issue on the Seville meeting.*

**COMMENT**

In the context of salvage therapy, where increasing the numbers of agents in a combination almost always increases the likelihood of a better response – largely due to a heterogeneity of resistance viral population during early failure – the increased number of drug-drug interactions, makes using TDM to manage treatment experienced patients essential.

In the UK this is facilitated by the validated laboratory service provided at Liverpool University, especially as costs of TDM are subsidised by the manufacturers of amprenavir (Agenerase), indinavir (Crixivan), lopinavir/rit (Kaletra), nelfinavir (Viracept) and saquinavir (Invirase, HGC; Fortovase, SGC).

References

5. G Peytavin, M Legrand, C Duvivier et al—Relationship between trough plasma concentrations of HIV antiretroviral drugs and virological response and mutations reversion in gighaart trial (anrs 097). XIV International AIDS Conference, Barcelona 7-12 July. Abstract TuPeB4568

Pharmacokinetics and further benefits of therapeutic drug monitoring (TDM)

Simon Collins, HIV i-Base

TDM to individualise indinavir/ritonavir dosing

TDM is routinely used in France for dual-PI combinations and patients in France have anecdotally been using lower dual-PI doses for many years on the basis of the results provided. Guiard-Schmid and colleagues retrospectively reviewed 153 patients using low dose ritonavir (RTV) with three doses of indinavir (IDV) from June 1999-December 2001. [1]

Forty-two patients were treatment naïve and starting their first therapy, 72 were switching dosing only from previous TID indinavir regimen, and 39 were changing to IDV/RTV as part of a new rescue therapy. All patients received 100mg RTV BID. Physician choice determined original IDV dose: 800mg BID (Group 1, 57%), 600mg BID (Group 2, 37%), 400mg (Group 3, 6%).

After a mean 13 months (± 6.8mo) duration of treatment and a median of three (1-9) IDV drug level samples, only 19% patients remained on the 800/100 BID dose. Dose reductions due to side effects and a high Cmax >10000 ng/ml, were performed in 70 patients (55 from Group 1, 14 from Group 2). 73% of naïve patients, 80% of switch and 31% of salvage patients had viral load <50 copies/ml at last test. Additionally, 14/27 patients with viral rebound on IDV TID prior to the switch recovered viral load <50 copies/ml.

Using TDM to individualise therapy in France appears to improve toxicity profile of the dual-PI combination and retain efficacy at lower doses to those generally recommended.

Food interaction with indinavir/ritonavir

A small study from Burger and colleagues in the Netherlands, similarly concerned with the higher Cmax and shorter Tmax of the 800mg/100mg indinavir regimen, analysed the PK effect of food in patients at steady-state dosing. [2] They report that taking RTV/IDV on an empty stomach increased Cmax by 19% without significantly affecting Cmin or AUC, and that neither the Cmin or AUC were adversely affected when taken with food. The recommendation for patients remaining on the 800/100 dose was therefore to take these medications with a light meal.

TDM for amprenavir/ritonavir

The relationship between amprenavir (APV) Cmin when given in combination with ritonavir and virological response was reported by Peytavin in a substudy from the Genophar Study which guided treatment choice by genotype. [3] A statistical relationship between Cmin at week 8 (though not at week 12) and both viral load at week 12 and change in viral load between weeks 0-12.

APV cut-off of 1250ng/ml was the best predictor of virological response (Spearman test, p=0.02) and IQ combining APV Cmin and mutation score were highly predictive of virological response at week 12.

TDM for lopinavir/ and amprenavir (and NNRTIs)

The interaction between amprenavir and ritonavir is complicated when using lopinavir, and further complicated when additional NNRTIs are included in a regimen. Yet these combinations are increasing used in salvage therapy, and review of these interactions from Reynolds and colleagues from Liverpool University again highlighted the utility of TDM. [5]

Adding LPV/r to APV/r resulted in a significant decrease in the median APV plasma concentration (p=0.05) despite an increase in APV dose. In a small cohort, the addition of an NNRTI further reduced the median APV concentration (p=0.03). LPV median plasma concentrations were significantly reduced by adding APV (p=0.005). However, the presence of an NNRTI had a lesser effect (p=0.22).

**APV concentrations (ng/ml):**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>APV600/RTV 100</td>
<td>9</td>
<td>1880</td>
<td>908-3610</td>
</tr>
<tr>
<td>APV 750/LPV400/RTV100</td>
<td>15</td>
<td>1113</td>
<td>510-2816</td>
</tr>
<tr>
<td>APV 750/LPV400/APV*</td>
<td>6</td>
<td>678</td>
<td>528-2278</td>
</tr>
</tbody>
</table>
LPV concentrations (ng/ml):

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPV 400/RTV 100</td>
<td>33</td>
<td>6295</td>
<td>1218-14452</td>
</tr>
<tr>
<td>LPV 400/RTV100/APV*</td>
<td>12</td>
<td>2878</td>
<td>822-9327</td>
</tr>
<tr>
<td>LPV 400/RTV100 + NNRTI</td>
<td>8</td>
<td>4683</td>
<td>667-18892</td>
</tr>
</tbody>
</table>

* 600-1200mg BID

The study concluded that is a complex PK interaction and given the marked interpatient variability highlights the potential importance of concentration monitoring (TDM).

TDM for newly reported interaction between lopinavir/r and nevirapine

A clinically significant interaction between lopinavir/r and nevirapine was reported by Degen and colleagues from Hamburg. Steady-state levels of LPV/r and concomitant NNRTIs were measured by liquid chromatography/mass spectrometry for efavirenz (n=4), nevirapine (n=2) and LPV/r without NNRTI (n=4). [4]

<table>
<thead>
<tr>
<th>Cmin</th>
<th>Cmax</th>
<th>Tmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>No NNRTI</td>
<td>5690 (1420-11200)</td>
<td>124000 (3920-17300)</td>
</tr>
<tr>
<td>EFV</td>
<td>7625 (2870-11200)</td>
<td>14100 (6990-17300)</td>
</tr>
<tr>
<td>NVP</td>
<td>3330 (1420-5240) *</td>
<td>8110 (12300-3920)</td>
</tr>
</tbody>
</table>

Compared to the EFV group, NVP pts. showed a 57% lower median Cmin and 43% lower median Cmax. In patients without NNRTI the median Cmin was 25% and Cmax 15% lower than in the EFV. The PK of NVP showed an 80% decrease of median Cmin and 77% of median Cmax compared with published data without LPV/r.

This study size, although tiny, shows the importance of individually monitoring drug levels for patients whenever interactions show a high degree of variability even when they have previously been well described. LPV/r levels were within an optimal range for all patients but suggest an increased dose of nevirapine and possibly a reduced efavirenz dose based on individual results. The study concluded that the results supported the use of TDM in clinical practice.

References:
2. R Aarnoutse, JWasmuth, G Fa&kuenhauer et al - Indinavir/ritonavir 800/100mg twice daily (BID) should be taken with food to prevent toxic indinavir peak plasma levels. XIV International AIDS Conference, Barcelona, 7-12 July. Abstract TuPeB4570.

HIV-associated malignancies in the HAART era: flickers of hope and understanding

Mark Bower PhD, FRCP, forHIVandHepatitis.com

The oncological themes of the World AIDS conference focused on the ways in which HAART has affected AIDS-related malignancies and their management including pre-invasive lesions of the cervix and anus.

There was little discussion in Barcelona of the management of Kaposi’s sarcoma and not a single abstract on primary cerebral lymphomas, reflecting the falling incidence of these tumours where there is access to HAART. It should, however, be recalled that Kaposi’s sarcoma remains the most common cancer in sub-Saharan Africa and its optimal management in a resource-poor setting has yet to be adequately defined.

The changing incidence of cancers since the introduction of HAART

It has been well established from individual cohort studies as well as meta-analyses that the incidence of the two most common AIDS-related malignancies, Kaposi’s sarcoma and non-Hodgkin’s lymphoma, have decreased since the era of HAART and a number of similar studies that reconfirmed this data were presented. [1, 2 and 3]
Some of these studies also addressed the incidence of solid tumours and have found increasing rates of these tumours since the beginning of the HAART era. For example bladder (Relative Risk = 1.58, CI=1.04-2.41) and prostate (RR=1.63, CI=1.32-1.99) cancers in the veterans’ study. [3] Similarly a UK cohort study found that seminoma, [4] and lung cancer [5] occurred at increased frequency in the post HAART era. Whilst the US women’s interagency HIV study also found an increased relative risk of lung cancer. [6]

However, data from US linked AIDS and cancer registries suggests that there is no clear relationship between the degree of immunosuppression as measured by CD4 cell count and the development of non-AIDS defining malignancies. [7]. Moreover, the multicentre AIDS cohort study (MACS) suggests that there has been a fall in the incidence of non-AIDS defining malignancies in the era of HAART. [8]

Advances in lymphoma therapy

Although the concomitant use of HAART has been associated with an improved overall survival in systemic non-Hodgkin’s lymphoma [9] and now also Hodgkin’s disease [10], it is suggested that this improvement represents an advance in the control of the infectious complications of the immune deficiency rather than better control of the tumour and that there is little evidence for improved tumour response rates.

New approaches that aim to achieve better tumour control have recently focused on the over-expression of the MDR-1 P-glycoprotein efflux pump by AIDS related lymphomas. Intriguingly the protease inhibitors are also substrates for this efflux pump that reduces intracellular concentrations of cytotoxic chemotherapy agents within the lymphoma cells.

One widely adopted strategy is the use of continuous infusions of chemotherapy including the widely used CDE regimen developed by Dr Sparano. An alternative approach is the use of liposomal encapsulation of anthracyclines to prolong their half-life and thus circumvent the protection given by the MDR-1 pump. Thus, Dr Levine has used a CHOP based schedule with the doxorubicin substituted by a liposomal version (TLC D99, Myocet) and has achieved a remarkably high complete response rate of 79% in a phase I/II trial that enrolled 23 patients. [11]

More aggressive approaches have also been advocated in response to the improved outcome of HIV infection since the introduction of HAART. It is against this background that the French and Italian group describe the favourable outcomes using the Stanford V regimen with HAART in patients with HIV-associated Hodgkin’s disease.

They achieved a complete remission rate of 81% in 59 patients and 25% subsequently relapsed. The actuarial overall survival and disease free survival at two years are 68% and 70%, respectively. [12] These results, although not as good as for the immunocompetent population, are considerably improved on the historical data from the pre-HAART era.

Similarly the use of high dose chemotherapy and autologous peripheral stem cell rescue for refractory or relapsed lymphoma is an established technique that until recently was deemed too aggressive for patients with HIV infection but that has now been introduced as an additional successful therapy for selected patients. [13]

Rituximab antibody therapy has also been found to be a useful addition to the therapy of aggressive B-cell lymphomas that express CD20 in the general population and is finding a role in refractory or relapsed HIV–associated non-Hodgkin’s lymphomas despite the prolonged B-cell cytopenia that follows this therapy. [14]

HAART and Kaposi’s Sarcoma

The mechanism of the falling incidence of Kaposi’s sarcoma (KS) and the response of the tumour to HAART remains uncertain. A direct anti-angiogenic effect of the protease inhibitors is described by Dr Ensoli using a murine model [15] and it is hypothesised that this accounts for the regression of KS with HAART.

However, a large clinical cohort study which confirmed the fall in KS incidence found that non-nucleoside reverse transcriptase inhibitor (NNRTI) based HAART was at least as effective as a protease inhibitor (PI) based regimen at preventing KS. They also found that most KS now occurred in antiretroviral-naïve patients and that patients developing KS whilst on HAART are usually experiencing treatment failure. [16]

Instead, this action may operate via the reconstitution of natural killer cell activity against Human Herpesvirus 8 which was demonstrated in vitro in peripheral blood monocytes from patients whose KS lesions had regressed on HAART therapy, also by Dr Ensoli’s group. [17]

Finally, anecdotal reports have described Kaposi’s sarcoma in the context of immune reconstitution. A report from Canada included three patients who developed severe visceral KS following the start of protease inhibitor-based HAART. This was associated with a rapid decline of plasma HIV viral load but no significant rise in CD4 cell counts. [18]

These conflicting data have failed to resolve the mechanism of KS regression and prevention by HAART and there is evidence for both indirect immunological mechanisms controlling HHV8 and a direct anti-angiogenic action on KS lesions.

Cervical and anal lesions

It has been widely recognised that HAART reduces the incidence of both KS and NHL where viral oncogenesis coupled to
immune deficiency have a recognised role in tumour pathogenesis. It was therefore thought that HAART might have a similar beneficial influence on both cervical and anal cancers and their precursor lesions.

Both tumours are associated with high risk genotypes of human papilloma virus (HPV) and are also found at higher frequency in other forms of immunosuppression. However the unfolding story in these epithelial tumours is less encouraging.

There appears to be no reduction in the development of human papilloma virus (HPV)-related cervical lesions in women who start on HAART with normal cytology at baseline and who are followed prospectively at six month intervals. There was no difference in the rate of development of lesions between women not treated with antiretrovirals, treated with reverse transcriptase inhibitors alone or with HAART, and all women had high rates of SIL (squamous intraepithelial lesions) (4-10%) at a mean follow-up of 40 months. [19]

In addition, HAART was a risk factor for cervical SIL in one study although this was not evaluated independently of the CD4 cell count. [20] Moreover there is no reduction in the HPV viral load in vaginal secretions in women following the start of HAART. [21]

The apparent lack of beneficial actions of HAART on pre-invasive anal lesions also increases the need to identify these lesions so that patients at risk of anal cancers can be monitored closely and treated at early stages. Although in this context the value of screening remains uncertain, the ability of anal cytological examination to pick up these lesions was confirmed in two abstracts. [22 and 23]

**HIV-associated lung cancer**

A large single institution cohort study of 8,636 HIV-positive patients (36,158 patient years of follow up) from the Chelsea & Westminster Hospital, London, has assessed the relative risk of lung cancer and compared it with the age and gender matched general population. They found that the relative risk was not increased during the pre-HAART era but the relative risk is 8 in the post-HAART era, suggesting a significant risk of lung cancer, a tumour not traditionally associated with immune suppression. [24]

This finding of a high relative risk of lung cancer during the HAART era is supported by an evaluation of mortality in HIV-infected patients at a US sub-urban hospital where 3/15 of the deaths were attributed to lung cancer. [25]

The poor prognosis described by Dr Powles is confirmed in a smaller study from California. [26] It remains to be seen how important non-AIDS defining tumours will become in the post-HAART era and how large a clinical burden they will represent.

The finding of an increasing incidence of these solid tumours, often developing after a prolonged period of HIV seropositivity and chronic immunosuppression, may also lead to a clearer understanding of the role of immune surveillance in common solid tumours such as lung cancer.

Dr Bower is Consultant Medical Oncologist, Chelsea and Westminster Hospital, London, UK.

References

All references are to the *Programme and Abstracts of the XIV International AIDS Conference. July 7-12, 2002. Barcelona, Spain.*

1. MP Carrieri and others. Reduced incidence of Kaposi’s sarcoma and of systemic non-Hodgkin’s lymphoma in HIV-infected individuals treated with HAART. Abstract TuPeC4728.
2. IE Salit and P Chantler. HIV-related Malignancies in the HAART era. Abstract ThPeB7310.
5. T Powles and others. HIV related lung cancer in the pre and post HAART era. Abstract WePpB2094.
7. SM Mbulaiteye and others. Immune deficiency and risk for malignancy among persons with AIDS. Abstract ThPeC7478.
8. EC Seaberg and others. The impact of highly active antiretroviral therapy (HAART) on cancer incidence in the Multicenter AIDS Cohort Study (MACS). Abstract ThPeC7484.
11. AM Levine and others. Liposomal doxorubicin (TLC D99, Myocet) in combination with cyclophosphamide, vincristine and prednisone is an active regimen for HIV associated lymphoma. Abstract WePpB2091.
14. LG Goelkel and others. HIV-related lymphoma: Rituximab concomitant to second-line chemotherapy following tumor progression under CHOP or early relapse. Abstract ThPeB7318.
15. C Sgadari and others. HIV protease inhibitors block angiogenesis and promote regression of Kaposi’s sarcoma. Abstract WePeA5760.
**Lopinavir/r exhibits sustained virologic response in antiretroviral-naive patients: 3-year data**

By Brian Boyle MD, for HIVandHepatitis.com

As part of a HAART regimen, lopinavir/r (Kaletra) appears to be a potent, effective and well-tolerated boosted-protease inhibitor combination (lopinavir/ritonavir). One of the initial studies evaluating Kaletra enrolled 100 antiretroviral-naïve, HIV-infected patients with a viral load >5,000 copies/mL and without any CD4 cell count restriction.

In this three-year prospective, randomised study of lopinavir/r, patients were randomised to receive one of three lopinavir/ritonavir doses, all of which were given twice daily (200/100mg; 400/100m; or 400/200mg) together with d4T and 3TC (both given twice daily) after either 3 weeks of lopinavir/r monotherapy (Group I) or from study entry (Group II). After 48 weeks, all patients were converted to open-label lopinavir/r (400/100 mg twice daily).

At week 156, 75% of patients had a viral load <400 copies/mL based on intent-to-treat, noncompleter=failure (ITT NC=F) analysis and 76% had viral loads <50 copies/mL at week 144 (ITT NC=F). Overall, at week 156, the mean CD4 cell count increased 356 cells/mm³, regardless of baseline CD4 cell count.

Fifteen patients experienced loss of virologic response (two consecutive viral load >400 copies/mL following any value <400 copies/mL or failure to achieve <400 copies/mL) through week 156 of which eight demonstrated resuppression either at week 156 or latest available visit without any change in therapy.

Genotyping and phenotyping data was available for six of the seven patients who never regained a virologic response: 0 of 6 had resistance in protease, and three of six had resistance to lamivudine (M184V/I mutation). Twenty-three patients discontinued therapy prior to week 156, five of which were due to reasons possibly related to study drugs (including one death 10 days post thoracic spinal surgery with perioperative MI).

At study entry, 36% of the enrolled patients had a CD4+ cell count <200 cells/mm³, but due to the significant CD4+ T cell count increases only 5% were still <200 cells/mm³ at week 156; similarly, while 56% had a baseline CD4+ cell count <350 cells/mm³, only 14% were still below that level at week 156. Of the five patients with CD4+ <200 cells/mm³ at week 156, two prematurely discontinued during the first 52 weeks due to noncompliance and the other three were on therapy for 144 to 156 weeks with baseline counts of 2-11 cells/mm³ and final counts of 159-192 cells/mm³.

The authors conclude that lopinavir/r, in addition to being safe and well tolerated, exhibits sustained virologic response in long-term follow-up in antiretroviral naïve patients with a significant and sustained increase in CD4+ cell count through 156 weeks regardless of baseline CD4+ cell count.


**Patients will have options regarding T-20 (Enfuvirtide) injection sites**

By Brian Boyle MD, for HIVandHepatitis.com

T-20 (Enfuvirtide) is likely to be the first of the “entry inhibitors” to be approved. This new class of antiretroviral drugs suppresses HIV replication by blocking one of a series of steps required for it to gain entry into the human cell. While other entry inhibitors block certain surface receptors, T-20 blocks gp41-mediated viral fusion to host cells.

The good news regarding enfuvirtide is that it has been shown in several studies, including two important studies presented...
at the XIV International AIDS Conference (TORO-1 and TORO-2), to significantly increase viral suppression and improve CD4+ T cell counts in HIV-infected patients on salvage antiretroviral therapy, i.e., patients that have failed multiple regimens and have limited further therapeutic choices.

The bad news regarding T-20 is that it must be injected subcutaneously (SC) twice daily. Further, while studies have shown that it is preferentially injected in the abdominal area, where there is very good absorption, T-20 absorption is complex and there has been concern that the location of the injection site may significantly impact its bioavailability. This could cause problems for patients since T-20 frequently causes a local site reaction, which may persist for days, and the ability to rotate sites may be extremely important.

In a study presented at the Barcelona AIDS conference, T-20 absorption was studied in a multiple dose, three-way randomised, crossover study. The study involved 12 HIV-1-infected patients who received 90 mg doses of T-20 twice daily at three different injection sites located either in the abdomen, thigh or arm, in three consecutive periods of seven days each. Serial blood samples were collected and levels of plasma T-20 and its metabolite concentrations were measured.

The investigators found that compared to the abdomen, absorption of T-20 in the thigh is comparable and in the arm is slightly better. Compared to the abdomen, the relative bioavailability of T-20 in the thigh is virtually the same (AUC12h 101%) and in the arm it is somewhat, but not significantly, higher (AUC12h 117%). Further, plasma concentrations of the T-20 metabolite were approximately 15% of the parent drug regardless of the site of injections, and the metabolite represents only “a minor constituent in plasma”.

Based upon these data, the authors conclude, “Because of comparability in absorption of T-20 from the three different SC injection sites, T-20 offers HIV-1 infected patients the freedom to rotate the site of injection.”


The role of tenofovir in antiretroviral-naive patients

Calvin J Cohen MD, MS, for thebody.com

This study was among the most discussed by at least some participants at the meeting in Barcelona, in part because of the impressive overall success of the study - representing perhaps another benchmark in terms of how well we can establish viral suppression in those just starting their first antiretroviral regimen.

The study design was to compare one of the more successful combinations noted to date — efavirenz (Sustiva) and 3TC (Epivir or lamivudine) were included in both arms of the regimen. The study compared using either d4T (Zerit, stavudine) or tenofovir (Viread) as the third drug in the regimen. The choice of d4T was made for several reasons, including data from several studies in the past showing that the combination of 3TC and efavirenz with most any third drug did very well, even at high viral loads and low initial CD4+ counts, and when these were combined with d4T, the success rates reported were very high, with a very low rate of initial gastrointestinal upset making it an attractive combination for patients getting started on therapy. Overall, the success rates of both arms were essentially identical for the number/percent of those who achieved viral suppression.

The baseline characteristics were notable because about 25% of the 600 people enrolled in this study were women. The average viral load was about 80,000, with a CD4+ count of about 280. Over the first year, only 1% of participants dropped off the study due to adverse events, a tribute to the success of both combinations. At the end of week 48, 87% of those in both arms had a viral load of less than 400 copies, and when they excluded those who did not have data at week 48, about 95% of those on both combinations had a viral load of less than 400 copies. Using the more rigorous 50 copy cutoff, about 82% had reached this degree of suppression when including all of those who enrolled, and while not presented, it is reasonable to estimate that about 90% had a viral load of less than 50 copies who had continued on the study for the entire time. Both groups had a similar increase in CD4+ count by about 170 cells. There was no difference in the success rates of these combinations for those who entered with a viral load above 100,000 copies, and similar success was noted for those with a pretreatment CD4+ count below 200/mm3.

In terms of safety, both arms did well. There were about 7% who had peripheral neuropathy of any severity by week 48 on the d4T arm, while only 2% had this occur while on tenofovir. There was a suggestion also of a difference in lipodystrophy (4% d4T vs 1% tenofovir) but this was not further described. There also was a difference in the blood lipids with higher values in both cholesterol (53 mg/dL vs 25 mg/dL) and triglycerides (74 mg/dL vs 0 mg/dL) for those on d4T compared to tenofovir respectively. There was no difference noted in kidney function, a concern for the class of drugs of which tenofovir is an example, nor was there any significant difference yet in serum phosphorus, another concern for these types of agents from prior studies.

This study clearly establishes the role for tenofovir as a component of an initial treatment combination. The high level of
success noted for both arms of this study also gives renewed confidence that our current regimens are amply potent, simple, and safe for the vast majority who take them. The suggestion of some potential safety advantages of tenofovir over d4T in terms of blood lipid differences will no doubt be the focus of future presentations of these data. While some physicians may prefer to await longer term data on any new medication to establish its multiyear safety track record, there is no information from other earlier studies to suggest a concern with the ongoing safety of tenofovir after a few years of use. Thus, it is likely this study will lead to the inclusion of the pairing of 3TC/tenofovir as an alternative nucleoside pairing in an initial combination. Of note, as with ddi/3TC, this combination has the advantage of both agents being one pill each, taken just once a day (although this study did not test the regimen in a once a day strategy, as the approval of the use of 3TC as a once daily agent occurred after this study was complete). With the recent availability of a 600 mg Sustiva tablet, the number of simple initial regimens that are very successful has just been expanded by a new arrival.

Ref: S. Staszewski, J. Gallant, A. Pozniak et al. Efficacy and Safety of Tenofovir Disoproxil Fumarate (TDF) Versus Stavudine (d4T) When Used in Combination with Lamivudine (3TC) andEfavirenz (EFV) in HIV-1 Infected Patients Naive to Antiretroviral Therapy (ART): 48-week Interim Results (LbOr17)
Source: www.thebody.com

Treatment interruption strategy reports from the XIV International AIDS Conference
Mark Dybul MD, for HIVandHepatitis.com

The meeting saw some shifts in how investigators currently view treatment interruption strategies, particularly those strategies for patients treated during chronic HIV infection.

A ‘debate’ on treatment interruption strategies including those for patients treated during acute and chronic infection as well as those in salvage therapy revealed remarkable consensus that, at this point, most strategies should not be applied broadly in clinical practice pending the results from ongoing studies.

There was also a remarkable lack of data presented on auto-immunization in chronic infection throughout the meeting and in the debate there was general agreement that auto-immunization as a strategy in chronic infection is not a viable clinical strategy. Yet there was much interest in many other treatment interruption approaches and much interesting data. Although the topic is becoming very diverse, with increasing overlap between topics, it remains easiest to divide things along the standard categories of acute, chronic and salvage.

Acute HIV infection
There is increasing evidence for a division of responses to treatment interruptions among patients treated during acute HIV infection, prior to seroconversion, and those treated during recently acquired HIV infection (generally defined as those within 90 days to six months of acute infection).

During the ‘debate,’ Bruce Walker [Abstracts WeOrA197 and ThOrB259] updated his group’s well-know study of 14 patients who were treated with HAART prior to seroconversion (or soon thereafter in two of the 14) for a mean of about a year and have since undergone 1-4 cycles of treatment interruptions of variable duration with resumption of HAART when the viral load exceeded 5,000 copies/mL three times or 50,000 copies/mL once.

Ten of 14 patients continue to maintain viral loads < 5,000 copies/mL for up to three years or more after one to four interruptions and eight of 10 maintain viral loads in the lowest quartile compared to data of patients in the MACS. This continued positive effect is not due to HLA B27 or B57 (known to be factors in long term non-progressors) and in fact several patients are HLA B35 positive (a known marker of rapid progression). Thus, there continues to be evidence for auto-immunization phenomena as a result of treatment interruptions in the majority of these patients treated with HAART during acute HIV infection, prior to seroconversion.

In contrast, Marty Markowitz [Abstract ThOrB260] presented his data from 16 patients treated during recently acquired infection (mean time from symptoms two months), five of whom received HAART alone and 11 of whom received HAART plus the vaccine candidate ALVAC.

In contrast to Walker’s patients, only two had significant CD4 T cell proliferation responses to p24 Antigen and all patients had a rebound of plasma viremia to relatively high levels within three weeks of treatment interruption that was indistinguishable from patients treated during chronic infection.

Interestingly, all patients had a peak viremia followed by nadir set-point viremia that decreased about 1.5 log10 copies/mL in both groups; this indicates the ability of the immune system to do a pretty good, if not complete, job of controlling HIV. Markowitz also showed an ebbing of virologic control over time with 10 of 12 patients having a viral load > 5,000 copies/mL after 21 months of treatment interruption.
In a similar way, Miro and colleagues [Abstract ThOrB1437] reported on 12 patients who initiated HAART within 90 days of infection and continued for greater than one year. All had viral loads < 20 copies/mL before beginning four cycles of two months off HAART followed by two-four months on HAART. Again, similar to the Markowitz patients, none of the 12 had CD4 T cell proliferation responses to p24 Antigen when HAART was initially started. During sequential interruptions, nought out of 12, four out of 12, four out of 12 and two out of six had viral loads < 3,000 copies/mL at the end of each interruption despite both CD4 and CD8 T cell responses increasing during interruptions.

Thus, there is increasing evidence for a different degree of auto-immunization effect in patients treated during acute versus recently acquired infection. This may have to do with the relatively rapid loss of HIV-specific CD4 responses since Walker’s patients have high responses while Markowitz and Miro saw low or absent responses.

In addition, a study by Vogel and colleagues of SIV [Abstract MoPeA3083] showed that 19 of 21 macaques infected with Mac239 had at least one CTL escape mutation during acute SIV infection. Therefore, it is possible that treatment early, but not during acute infection, may lead to immunologic losses that limit the auto-immunization effect. In the debate session, Walker and Markowitz gave good summaries of the potential pros and cons of early therapy including a potential for auto-immunization for those treated very early and also possible limitation of the evolution of HIV in many quasispecies that may be reflected in the escape mutations. There was general agreement that more studies were needed.

Finally, and very importantly, Walker presented follow-up on a patient in his group’s studies who was doing very well with control of plasma virus to < 5,000 copies/mL for around 1,000 days who had then had a rebound to >50,000 copies/mL. The initial suspicion was viral escape, but after sequencing the virus itself it was discovered that the patient had been super-infected with another virus (that was 12% different than the original virus the patient had been infected with) and had a sexual history that was consistent with super-infection. Thus, a patient who could control one virus very well had difficulty controlling a new virus. These data, combined with those from Vogel, indicate the significant challenges for vaccine, and therefore, therapeutic immunization, strategies.

**Chronic infection: Auto-immunization**

As noted, there were almost no reports of auto-immunization studies in chronic HIV infection. In the debate session Gunthard [Abstract ThOrB262] gave further evidence from the SITT study that auto-immunization is likely to have limited clinical significance in patients treated during chronic infections with the response rate around 15%. In addition, he provided interesting evidence that the proviral DNA levels may help predict responders and non-responders, and that the CD8 CTL response levels do not correlate with the ability to control virus: good evidence for a lack of significant auto-immunization effect.

In addition, Garcia [Abstract ThOrB1438] presented data from 44 patients treated during early chronic infection who underwent treatment interruptions. Comparing the responders (viral load <5,000 copies/mL and >0.5 log10 copies/mL decrease compared to baseline) to non-responders, they found that a combination of low CD4CD38 and naïve cells and a high memory cell count with good proliferation responses to tetanus toxoid and p24 Antigen predicted responders 97% of the time.

There were several presentations that may explain the lack of auto-immunization effect in many patients treated during chronic HIV infection.

Poccia [Abstract ThOrB1442] presented a study of 26 patients who underwent a single treatment interruption of one month followed by re-initiation of therapy and evaluated patients who had delayed versus rapid viral rebounds. Those who had delayed rebounds did not have evidence for significant increases in HIV-specific responses, indicating that the slow rebound was not related to high levels of immune response. In contrast, patients with rapid rebounds of viral load did have significant increases in CD8 T cells producing IFN-gamma. However, when these cells were analyzed, they were mostly CCR7-CD45RA- , an indication of pre-terminally differentiated, or less effective, CTL responses.

In addition, Oliva and colleagues [Abstract ThPeA7135] showed that in these same patients an increase in viral load was associated with a significant decrease in NK cell secretion of IFN-gamma, indicating significant dysfunction, that was restored when HAART was resumed.

Finally, Van Lunzen [Abstract ThOrA1180] showed that, while there is a broadening of CTL responses to HIV in the periphery following treatment interruptions in chronic infection, there was no significant broadening of responses in CTL responses isolated in lymph nodes in most patients evaluated. Thus, in chronic HIV infection, auto-immunization may fail due to poor qualitative CD8 and NK cell responses during treatment interruptions.

**Less total time on therapy**

At this conference, there seemed to be a real shift from using treatment interruptions in chronic HIV infection for auto-immunization to using these interruptions for the sole purpose of reducing time on therapy. This strategy is employed to try to reduce time on therapy, and therefore diminish the unwanted toxicities and decreases in quality of life in patients. The most clinically relevant of these approaches in resource rich settings may be stopping therapy in patients who started HAART under previous guidelines who would not meet current recommendations for starting therapy.
Gallant [Abstract ThOrB1439] presented his group’s study of 101 patients. Originally, the study included only patients who never had a CD4 count < 200 or an OI. However, in the current cohort, 21 patients had AIDS—defining criteria. 68 of 101 (67%) patients, with a mean CD4+ T cell count of 483 cells/mm3 and a mean viral load of 12,439 copies/mL, have been on ARV therapy for a mean of 62 weeks.

The greatest predictor of remaining off therapy was a CD4 T cell count > 350 cells/mm3 PRIOR to initiating HAART. The viral load prior to therapy was not a significant predictor of resuming therapy. Similarly, Kroliewiecki [Abstract ThOrB1440] presented data on 28 patients who started HAART with CD4 > 350 cells/mm3 and had been on ARV therapy for > 6 months. Half of the patients remained on continuous therapy and half discontinued HAART.

At 24 weeks, in the discontinuation group the CD4+ count had dropped from 610 to 544 cells/mm3 but the LDL cholesterol also dropped from 132 to 90 mg/dL; there was no significant change in either marker in the continuous group. Although two patients resumed HAART, one patient in the continuous arm stopped due to toxicity. Thus, relatively long-term interruptions may be safe in patients who began therapy when the CD4 T cell count was > 350 cells/mm3, but patients need to be monitored carefully for declines in CD4 counts.

In contrast, there were numerous reports confirming that treatment interruptions in patients who have controlled viremia but CD4 counts <200 cells/mm3 can lead to significant drops in T cell counts and even clinical events. Finally, Fumaz and colleagues [Abstract ThPp2135] showed a significant increase in quality of life in patients who underwent a single interruption.

In contrast to single interruptions for patients with high CD4+ counts, multiple interruptions may not have a significant benefit and may carry risks of resistance.

Dybul [Abstract ThOrB2621] showed data from a study of 24 patients randomized to maintain continuous HAART and 21 who underwent cycles of four weeks off HAART and eight weeks on HAART. While at week 40, after the fourth off HAART period, there was a significant reduction in total and LDL cholesterol and triglycerides in the intermittent compared to the continuous arm, by week 48 (or 8 weeks back on HAART) there were no significant differences between the groups.

In this regard, although it was in 12 patients treated during primary HIV infection, Milinkovic and associates [Abstract TuPeB4532] evaluated lipid levels in patients who underwent four cycles of two months off followed by two-four months on HAART. During the period of continuous therapy for a year after diagnosis, triglyceride and cholesterol levels increased 70% and 46%, respectively. During interruptions, triglyceride levels decreased 23% and cholesterol 12% (which was not significant) but rose to baseline levels during resumption of treatment.

However, short cycle therapy that does not allow for viral rebound still looks good. Dybul updated the NIH pilot study: eight patients who remain on a study of seven days off/ seven days on HAART with Zerit (stavudine) + Epivir (lamivudine) + Crixivan (indinavir)/Norvir (ritonavir) are maintaining suppression of plasma viremia to < 50 copies/mL with infrequent blips of < 500 copies/mL in some patients, for 72-104 weeks.

In addition, the significant reductions in LDL and total cholesterol and triglycerides that had been reported up to 24 weeks have been extended to 53 weeks and up to 72 weeks in those that have been evaluated. Dybul noted that the clinical application might be limited due to difficulties with adherence. In this regard, he reported an eight person pilot study of seven day on/seven day off therapy with a once a day regimen of Videx (didanosine) + Epivir + Sustiva (efavirenz). Out to 24-40 weeks, there has not been a single value > 50 copies/mL.

However, Gunthard showed that in approximately 50 patients evaluated at day seven of the initial interruption in the SITT study, a substantial number had > 50 copies/mL. There was no clear explanation for the discrepancy: Dybul noted in the discussion that they had evaluated approximately 70 patients and had not found any patients with a significant rebound at day seven.

**Salvage therapy**

Two large, controlled studies have been completed. Unfortunately, they have conflicting results.

Katlama and colleagues [Abstract WePeB5887 and ThOrB263] presented data from the GIGHAART study, which evaluated immediate six-seven drug salvage therapy versus a treatment interruption of eight weeks followed by six-seven drug salvage therapy in 70 patients; the endpoint was viral load changes at weeks 12 and 20 (i.e., after all patients had been on 12 weeks of GIGHAART). The delayed group did substantially better with 26% vs. 62% having > 1 log10 copies/mL reduction in viral load (mean –0.37 vs. –1.91 log10 copies/mL), and 15 % vs. 38% < 400 copies/mL.

However, Clotet [Abstract ThOrB264] presented the Retrogene study of salvage with triple PIs – Norvir + Fortovase (saquinavir) + Kaletra (lopinavir/ritonavir) – on an NRTI backbone in patients randomized to receive a treatment interruption or not. At 48 weeks there was no difference in viral loads between the interruption vs. non-interruption groups.

The differences in the studies may relate to the number of mutations at baseline (more in the Katlama study so interruption maybe more helpful) or the duration of follow-up, but the data are unclear at this point regarding the benefits of interrupting therapy in patients with a highly-resistant virus starting antiretroviral salvage therapy.
New data from clinical trials of antiretrovirals

Charles Hicks MD, for HIVandHepatitis.com

As has been true for most of the major HIV conferences over the past 10 years, presentations from the XIV International AIDS Conference in Barcelona included results from several important antiretroviral therapy clinical trials. While there were no blockbuster breakthrough studies, newly presented data helped clarify some important issues related to antiretroviral therapy. Most of the studies involved either treatment-naïve patients or fairly heavily pre-treated patients.

Clinical trials in treatment-naïve patients

The CLASS study

John Bartlett from Duke University presented results from the GlaxoSmithKline-sponsored ESS40001 trial, also known as the CLASS study. The primary objective of this trial was to compare drugs from different classes of antiretroviral therapy when paired with a nucleoside backbone of abacavir (ABC) and lamivudine (3TC). The third drug was stavudine (d4T), efavirenz (EFV), or ritonavir-boosted amprenavir (APV/r). Data presented were from a planned 48-week analysis. [Importantly, the ultimate objective of this study is to assess two-year outcomes including the efficacy of preplanned sequencing of regimens for those experiencing virologic failure of initial therapy. This portion of the study is ongoing.]

A total of 297 patients enrolled in the study, and the treatment arms were well matched demographically (notably, about 70% of the patients enrolled were black or Hispanic). Median baseline viral load at entry was 4.9 log10 copies/ml and median entry CD4 count was around 300 cells/mm3. Intent-to-treat (ITT) and on treatment (OT) analyses are shown below. For the <50 copy assay, there was a significant difference favoring the EFV arm over either of the other treatment arms in the ITT analysis.

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>&lt;400 copies (ITT)</th>
<th>&lt;400 copies (OT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>d4T (NRTI)</td>
<td>80%</td>
<td>90%</td>
</tr>
<tr>
<td>APV/r (PI)</td>
<td>75%</td>
<td>91%</td>
</tr>
<tr>
<td>EFV (NNRTI)</td>
<td>83%</td>
<td>98%</td>
</tr>
</tbody>
</table>

Virologic suppression (using a 50 copy assay) among patients with baseline viral loads above 100,000 copies/ml were also significantly better in the NNRTI arm (EFV = 77%, d4T = 55%, APV/r = 53%). CD4 lymphocyte increases were in the range of 173 to 196 cells/mm3 and were not significantly different among the three arms of the study.

While these 48-week data support the use of efavirenz-based regimens for treatment-naïve patients, it is worth noting that the two-year outcome is the primary objective of this trial. Important treatment strategy issues including successful sequencing and “salvageability” have yet to be delineated.

ACTG 384 study

This study in many ways illustrates the unique strengths of the AIDS Clinical Trials Group (ACTG) as well as some of its weaknesses. Strengths include the large numbers of patients enrolled, the considerable scientific rigour in the design and conduct of the trials, and the meticulous impartiality of the results. Weaknesses primarily relate to the considerable bureaucracy that must be accommodated to get a big study underway.

This latter issue often means that there are substantial delays from study concept to patient accrual to study analysis. Moreover, the review process for ACTG proposals often adds considerable complexity to study designs. Thus, by the time some ACTG trials are presented, study designs often seem surprisingly outdated, and interpretation of results can be challenging.

ACTG 384 was a study with a fairly complex design that was intended to address three main questions: 1) Is zidovudine (ZDV) + 3TC better than d4T + didanosine (ddI) as the nucleoside backbone of ART in treatment-naïve patients? 2) Is an NNRTI (EFV)-based regimen better than a PI (nelfinavir [NFV])-based regimen? 3) Is a four-drug regimen (using both EFV + NFV)
that uses drugs from all three classes superior to a three-drug, two-class regimen?

The study enrolled 980 ART-naïve patients in the U.S. and Italy to try to answer these questions. The study was set up as a factorial design, which means that there were six treatment arms that contributed to the results with the various questions being answered by combining results across the regimens.

The design specified second-line regimens for patients failing initial therapy if they were randomised to a three-drug regimen initially. The primary outcome measurement was the time to failure of the initial regimen for patients on the four-drug, three-class arms, but was time to failure of a second regimen for those initially treated with a three-drug, two-class regimen. This outcome was chosen to assess the durability of treatment in terms of the time until patients experience failure to all three classes of ART.

At entry, median baseline viral load was around 87,000 copies of RNA/ml and median baseline CD4 count was 278 cells/mm³. Median follow-up was 28 months. The statistical analysis of the factorial design was quite complex.

The results suggested that better responses were seen with ZDV + 3TC as the nucleoside backbone and with EFV as the third drug of the three-drug regimens. Much of the difference in outcome appeared to be a consequence of excess toxicity in the d4T + ddI arm.

Importantly, the overall interpretation is conditional, however, in that the superiority of the ZDV + 3TC combination was only seen when EFV was the third drug, and the superiority of EFV was only seen when it was given with ZDV + 3TC, and not when given with d4T + ddI. Moreover, the four-drug arms were superior to the three-drug arms, but only when all the three-drug arms were combined for comparison.

The four-drug arms were not superior to the best of the three-drug arms (ZDV + 3TC + EFV). There were no significant differences in CD4 lymphocyte changes among any of the arms.

Thus, this large and complicated study produced an increasingly familiar outcome – ZDV + 3TC + EFV is an excellent initial regimen for ART-naïve patients. This was an initial analysis of a wealth of important data and we are sure to hear more results from this trial in the future.

**Gilead 903 study**

A review of virologic outcomes in HIV treatment trials over the last five years shows that the proportion of patients achieving viral suppression below the level of detection has slowly but surely increased with the passage of time. This probably reflects improvements in drug potency, in ease of administration, and in drug pharmacokinetics, as well as an increased emphasis on patient adherence.

Results presented at this meeting from the Gilead 903 study continued the trend of improving HIV suppression and raised the bar even higher in terms of what the target ought to be for virologic success among treatment-naïve patients initiating a first HAART regimen.

The study was conducted at 81 sites in the U.S., Europe, and South America and was designed to compare tenofovir (TDF) to stavudine (d4T) when combined with 3TC and efavirenz. Six hundred patients were enrolled in this randomized, double-blind, placebo-controlled study to receive either d4T + 3TC + EFV or TDF + 3TC + EFV.

The mean viral load was 4.9 log10 and the mean CD4 count was 279 cells/mm³. By an ITT analysis in which missing values were counted as failures, both arms achieved 87% suppression to <400 copies RNA/ml at week 48 of follow-up. Using a 50 copy RNA assay, 82% of the TDF patients and 81% of the d4T patients achieved undetectable viral load at week 48. CD4 increases were 169 and 167 cells respectively. Both arms had about 9% of patients discontinuing study therapy, in most cases because of “lost to follow-up” or withdrawal of consent.

Discontinuations due to study drug-related adverse events were uncommon. Efficacy in patients with viral loads above 100,000 copies and with CD4 counts below 200 cells/mm³ was similar to those with less advanced infection.

These data are quite impressive and attest to the tolerability and convenience of both of these regimens. This study adds further evidence of the value of efavirenz and lamivudine as part of initial antiretroviral regimens, and establishes TDF as equivalent to d4T as part of the nucleoside/tide backbone of HAART regimens.

Future trials of antiretroviral regimens for treatment-naïve patients will need to achieve similarly impressive results to be placed alongside these therapeutic choices.

**EFAVIP-2 study**

In addition to the data reviewed above regarding the use of efavirenz in treatment-naïve patients, there was one additional study that was of considerable interest to clinicians treating patients with advanced HIV infection. This trial, called “EFAvirenz in Very Immunosuppressed Patients” [or, EFAVIP-2] assessed a population of treatment-naïve patients with baseline CD4 counts <100 cells/mm³ who initiated therapy with efavirenz (n = 92) or a non-boosted PI (n = 218).
The data was drawn from three large patient cohorts in Madrid, Spain, and the study was intended to help determine the appropriate treatment strategy for patients with advanced HIV infection as determined by low CD4 lymphocyte counts at HAART initiation. Median CD4 counts were 34-39 cells/mm³, and median viral load was >250,000 copies RNA/ml.

Of potential importance in interpreting the results, the patients treated with efavirenz were significantly more likely to also be on ZDV + 3TC while those on PI therapy were more likely to be receiving ddi + d4T. Probably at least in part due to this difference in nucleoside backbone, there were significantly more discontinuations due to adverse events in the PI arm (23.8% versus 8% in the EFV arm).

There were also more discontinuations due to virologic failure in the PI group (12.8% in the PI arm versus 4.3% in the EFV arm). When analysed by time to treatment failure, the two treatment strategies diverged by about six months with improved outcomes being observed in the EFV arm at all subsequent time points. Similarly, CD4 increases were significantly greater in patients receiving EFV.

While the differences observed were impressive, the study was a retrospective analysis, and, as such, is subject to several limitations. Most importantly, the study was not randomised, which makes selection bias a very real potential issue. Additionally, the PI regimens were not ritonavir-boosted and thus not reflective of most PI-based HAART currently used. Despite these reservations, this study provided valuable data supporting the efficacy of EFV in patients with advanced degrees of immunosuppression.

Clinical trials in treatment-experienced patients

Data from trials of treatment-experienced patients was not generally as compelling as that from treatment-naive patients. There were, however, some very interesting data presented on the use of T-20, the first fusion inhibitor, as well as on a PI-only regimen that avoided the use of RT inhibitors.

TORO-1 and TORO-2

T-20 (now also known by the tongue-twisting name "enfuvirtide") is the first entry inhibitor to reach late stages of clinical development. The drug works by blocking viral fusion with cell envelope and is administered by subcutaneous injection. It is close to achieving regulatory approval in parts of the developed world.

Two important trials (termed the TORO studies for "T-20 versus Optimised Regimen Only") were undertaken to obtain this approval and the results from these studies were presented in Barcelona. Both studies tested the efficacy of T-20 in heavily pre-treated patients experiencing virologic failure. Entry criteria required treatment experience with all three classes of drugs and a viral load >5000 copies RNA/ml.

All patients received an optimised salvage regimen of antiretroviral agents based on clinical history and resistance testing and were randomised to an optimised ART regimen alone or to an optimised regimen plus open label T-20 given at a dose of 90mg SQ q12h.

TORO-1 was conducted in the U.S. and enrolled 491 patients. Patients were very treatment-experienced and had advanced HIV infection. They had received a median of 12 prior antiretroviral agents over seven years of therapy, and 87% had experienced an AIDS-defining condition. Median viral load was 5.2 log10 and median CD4 count was 80 cells/mm³.

A total of 326 patients were randomised to the T-20 arm and 165 to the optimised therapy only arm. There was a significantly greater reduction in viral load in the T-20 arm: -1.70 log10 copies versus –0.76 log10 copies in the optimised therapy only arm. At 24 weeks, 37% of the T-20 patients had viral load <400 copies RNA/ml compared to 16% in the optimised therapy only arm.

Although injection site reactions were near universal, treatment discontinuations did not differ between the two arms: 11.3% in the T-20 arm and 10.9% in the optimised therapy only arm.

TORO-2 was almost identical in design. Five hundred and four patients with more than three months of experience with all three classes of antiretroviral agents were randomised to optimal therapy alone or optimal therapy plus T-20. At week 24, the patients receiving T-20 had a mean decrease in viral load of -1.43 log10 copies versus -0.65 log10 copies in the optimised therapy only arm. At 24 weeks, 37% of the T-20 patients had viral load <400 copies RNA/ml compared to 16% in the optimised therapy only arm.

Although injection site reactions were consistent with one another and demonstrated impressive antiretroviral activity through 24 weeks. This is welcome news for the ever-growing population of HIV-infected patients who have continued viral replication despite having received therapy with all currently available classes of agents. It remains to be seen what the long-term efficacy and tolerability of this injectable agent will be, but for now, the substantial potency of this drug is encouraging.

LPV/r + SAQ

A variety of approaches have been advocated to manage patients who have experienced multiple drug failure including treatment interruption on one extreme and “mega-HAART” on the other.
A small study by Schlomo Staszewski and colleagues suggested another option, that of a dual boosted PI, RTI-sparing regimen. In this study, 33 patients with multiple drug failure were given lopinavir/r + saquinavir. The rationale for this approach came from resistance testing in these patients which demonstrated potential susceptibility to both protease inhibitors with little evidence for susceptibility to any of the available reverse transcriptase inhibitors.

At the time of the switch, the median viral load was 5.2 log10 copies and the median CD4 count was 157 cells/mm³. After 24 weeks of follow-up, the median decline in viral load was −3.5 log10 and the median increase in CD4 count was +159 cells/mm³. An amazing 82% achieved viral suppression to below 400 copies and 58% were below 50 copies.

The dual PI therapy was relatively well tolerated with 73% still on the drug regimen after a median of 29 weeks of follow-up. While this is certainly a very selected population, the impact of this regimen was quite dramatic in these patients.

Dr. Hicks is Associate Professor of Medicine in the Division of Infectious Diseases, Associate Director of the Duke University AIDS Research and Treatment Center, Durham, NC, and a Contributing Editor to HIV and Hepatitis.com.

Source: http://www.hivandhepatitis.com
Copyright: hivandhepatitis.com

---

**IMMUNOLOGY AND BASIC SCIENCE**

**Behind the headlines about vaccine research**

*Gareth Hardy, HIV i-Base*

The basic science content of the XIV International AIDS Conference was considerably less than that of previous years. While much of the focus of this conference seems to have shifted since Durban 2000 to a more political and humanitarian theme, the majority of the science data currently being reported appears to be presented at the Conference on Retroviruses and Opportunistic Infections, the Keystone Symposia and other smaller meetings.

While a diversity of relevant and interesting oral and poster presentations provided updates on developing research topics, new and novel findings were somewhat thin on the ground. The over riding feeling prevalent at this Conference, even for those following the track A basic science, was one of “business as usual”. Suffice to say there was no major ground breaking data presented.

Of course one of the greatest implications of bringing together 14,000 delegates from just about every country in the world is the huge amount of press attention generated. This may serve to greatly enhance the dissemination of literature, statements, statistics and data, much of which reaches the press’s attention because of the glossiness of the brochures, pamphlets and press releases produced by its protagonists.

A clear example was the thunderous headlines inspired by the Thai AIDS Vaccine Evaluation Group and the US Military HIV Research Programme’s announcement that they are to initiate the world’s biggest phase III preventative HIV-1 vaccine trial at the end of this year: 16,000 volunteers between the ages of 20 and 30 years are to be recruited over one year and followed up for a further three years in what is expected to be a five year trial, ending in 2007. Half the volunteers will receive Aventis Pasteur’s canary pox vector expressing clade E gp120 and clade B gp41, together with gag proteins and protease. Clade E virus is the predominant viral subtype in Thailand. (ALVAC vCP1521) which will be administered at months nought, one, three and six with VaxGen’s whole gp120 (clade B and E) preparation (AIDSVAX B/E) as a booster at months three and six in. The other half will receive placebo at each of the four time points. “Thailand has a long commitment to develop ways to stem this epidemic, and a viable vaccine approach is key to that end” says Dr Vallop, director general of the Department of Communicable Disease Control, Thailand Ministry of Public Health. “The phase III trial is a milestone in the long journey toward an AIDS vaccine.” Says Dr Deborah Birx, director of the US Military HIV Research Programme.

Harriet Robinson of the Yerkes Regional Primate Research Center, Atlanta, USA, presented data on a successful DNA prime, MVA boost system in macaques. Prior studies had determined that this strategy was superior to DNA alone or DNA followed by a whole protein vaccine. Robinson’s team compared the ability of a gag-pol DNA/MVA SHIV vaccination strategy to protect macaques from disease following challenge, to a gag-pol-env DNA/MVA strategy. Animals were challenged at seven months after the boosts with two viral isolates to which cross neutralising antibodies do not occur. The gag-pol construct strategy failed to protect the animals from disease progression as no viral control was seen. However the gag-pol-env construct protected from disease and gave rise to stable control of viraemia and maintenance of normal CD4 T cell numbers in vaccinated animals. Thus the benefit of this construct showed that the env component was important in eliciting immune control following infection. Because of this a whole gp120 preparation was added, modifying the gag-pol-env DNA/MVA regimen. Surprisingly this resulted in loss of control of viraemia and loss of CD4 T cell numbers in these animals. Thus the addition of a whole gp120
preparation abrogated the protection induced by the DNA/MVA vaccine. Further investigations led to the discovery that this gp120 preparation induced the production of non-neutralising antibodies which enhanced SHIV infectivity/pathogenicity which the authors suggested may have contributed to the loss of control of virus in these animals. (WeOrA213)

This effect of a soluble envelope protein preparation may have implications for other similar vaccine strategies, including the phase III prophylactic vaccine studies proposed in Thailand. Indeed one poster presentation by Chien et al showed that in 14 matched pairs of HIV-1 infected rapid and slow progressors antibodies to the CD4 binding domain of gp120 were significantly higher in the rapid progressors compared to the slow progressors, again suggesting a role for such antibodies in enhancing pathogenesis (MoPPaA2001). This confirms work previously published by other groups, where higher envelope specific humoral responses are associated with increased risk of disease progression. Taken together these data suggest that while neutralising antibodies to the viral envelope proteins may yet yield an effective means of controlling HIV-1 infection, induction of non-neutralising envelope specific antibodies may have precisely the opposite effect. This is likely to be a very serious consideration for vaccine design and development. However, Thongcharoen presented results from a phase II, double blind, randomised placebo controlled trial of the Thai vaccine candidates (ALVAC cp1521 and AIDSVAX B/E) where intramuscular injections were given at 0, 4, 12 and 24 weeks (vaccine n=46, placebo n=15). Neutralising antibodies specific to the envelope of clade B lab strain SF2 were found in 27% of vaccinees and to clade E strains in 96% of vaccinees. CD4 lymphocyte proliferative responses to clade B envelope were also detected in 76% of vaccinees and to clade E envelope in 89% of vaccinees. Cytotoxic T cell responses were not yet evaluated (TuOrA1225).

Further evidence leaned toward the belief that mucosal HIV-1 envelope specific IgA antibodies may be protective of infection. In a study by Kebba et al vaginal secretions were collected and assayed for HIV-1-gp160-specific IgA and IgG antibodies from a cohort of eight Ugandan exposed seronegative (ESN) females with a history of frequent unprotected sexual intercourse with an HIV-1 infected spouse in addition to seven seropositive females (SP). Kebba found that while gp160-specific IgG was not apparent in the vaginal secretions of ESN females, it was readily detectable in six of the seven SP females. Although all ESN females were negative in two HIV serological tests for plasma IgG and negative for HIV-1 proviral DNA gp160-specific IgA was detectable in vaginal secretions and furthermore tended to increase concurrently with increasing plasma viral load in their infected spouse. Whereas IgA in SP females was inversely correlated with autologous plasma viral load. (MoOrA1053)

Jay Levy presented interesting results building on previous work by his group where interferon-a/b producing plasmacytoid cells (IPCs) were found to inversely correlate with viral load and AIDS defining disease. These CD11C+ plasmacytoid dendritic cells are the body’s main interferon-a producing cell. Because they express CD4 and both CCR5 and CXCR4, purified IPCs (>999.5%) were exposed to SI or NSI isolates and stimulated with soluble CD40L to assess their susceptibility to infection. While IPCs could be infected with HIV-1, viral replication in these cultures was found to be minimal, suggesting that they are not major producers of virus. Furthermore infected IPCs did not loose viability, suggesting that they are not killed by HIV-1 and may thus represent an important viral reservoir. In contrast HSV was found to cause loss of viability of IPCs in culture. Following the addition of activated CD4 T cells to IPC cultures, HIV-1 virus was readily recovered, up to seven days post exposure. This transfer of virus to CD4 T cells was found to be independent of DC-SIGN. In addition exposure to free virus did not induce IFN-a production by IPC, whereas exposure to HIV-1 infected CD4 T cells was a potent inducer of IFN-a production.

Levy showed that long-term non-progressors have higher numbers of IPCs than normal progressors and that in normal progression IPCs correlate with CD4 T cell numbers. However a very understudied population of HIV-1 infected individuals who remain disease free for extended periods of time without antiretroviral therapy despite very low CD4 T cell counts appear to have normal numbers of IPCs. Levy suggested that IPCs may thus have a role in protecting from disease if they are sufficient in number in advanced HIV-1 infection. (TuOrA1136)

Nobile et al described analysis of CD4 and CD8 T cell dysfunction during the natural course of HIV-1 infection, using premade cDNA expression arrays spotted with 111 genes associated with cell cycle regulation. Gene expression patterns were compared in CD4 and CD8 T cells between eight uninfected donors, eight HIV-1 infected patients and in cultured T cells stimulated with anti-CD3 and anti-CD28 over 60 hours. While increased expression of cell activation markers such as tyrosine kinases and cell cycle markers such as cyclins and CDKs (cyclin dependent kinases) were observed in uninfected donor CD4 and CD8 T cells after in vitro stimulation, the same pattern was observed in HIV-1 infected patients CD8 T cells only. CD4 T cells of HIV-1 infected patients demonstrated increased kinase expression, suggesting increased cell activation, but specifically lacked expression of the CDK2 gene, crucial to cell cycle progression from G1 phase to S phase. Furthermore, expression of the pro-apoptotic mdm2 gene was elevated in CD8 T cells of HIV-1 infected patients, but not CD4 T cells. This data suggests that while both CD4 and CD8 T cells are hyperactivated in HIV-1 infection, CD8 T cells are actively cycling, whereas CD4 T cells are anergic with a cell cycle blockade. (WeOrA1344)

Lending further support to this notion was a presentation by Yassine Diab et al who used newly available HLA DR tetramer/ HIV-1-peptide complexes with CFSE to identify functional antigen specific CD4 T cell clones in 20 HAART treated patients with primary HIV-1 infection and over three subsequent years of infection. In five out of seven of these patients who were treated early, tetramer stained HIV-1 specific CD4 T cells were detectable and cycled normally as measured by CFSE staining. 80% of these early treated patients maintained these responsive CD4 T cell clones over the study period. However in 11 late treated
patients, although tetramer stained HIV-1 specific CD4 T cells were evident, these did not stain for CSFE, demonstrating cell cycle blockade and clone specific T cell anergy. (WeOrA1346)

The clinical implications of this were perhaps illustrated in a presentation by Lange et al in which 29 patients receiving HAART with HIV-1 RNA <400/ml for at least nine months and a CD4 count > 450 were assessed to see if their CD4 nadir before receiving HAART effected their ability to mount antibody and recall lymphocyte proliferative responses following immunisation with tetanus, diphtheria typhoid or KLH. Responses were measured at the time of immunisation and four weeks later. An immune response score (IRS) was calculated from the antibody concentration, lymphocyte proliferative response and delayed hypersensitivity reactions induced by each vaccination. Patients were stratified according to whether they had experienced a pre-HAART CD4 count nadir of <250 cells or not. Although there were no differences in the CD4 counts at the time of vaccination (744 cells in the low nadir group and 724 cells in the high nadir group) there was a marked impairment of the IRS in the low nadir group (p=0.005). There was a linear relationship between the IRS and CD4 cell nadir at levels between 150 and 450 cells (r=0.6, p=0.01), but no relationship was apparent with CD4 count at the time of vaccination. This suggested that even when good immune reconstitution occurs in terms of CD4 counts and control of viral load is maintained, the CD4 nadir, and thus level of progression, prior to HAART predicts the response to vaccination while current CD4 count does not. (LbOr09)

Gotch et al presented a study where 36 patients treated with HAART for 17 weeks were randomised to receive either four injections of the whole killed HIV-1 gp120 depleted immunogen (Remune) three monthly, three cycles of IL-2 for five days four weekly, a combination of the two or just continued HAART. The mean CD4 T cell count of these patients prior to HAART was 303. Again CD4 lymphocyte proliferative responses to the vaccinating agent, or to other HIV-1 antigens, were not induced, even with the addition of IL-2. However it was noted that transient viral blips associated with each cycle of IL-2 in this study, were much less apparent in those patients receiving Remune with IL-2. (ThOrA1483)

An analysis of peripheral and lymph node CTL responses before and during a structured treatment interruption study by Van Lunzen et al may shed some light on why CTLs induced by STI in chronic infection fail to suppress viral load. In this study 15 individuals with <25 HIV-1 RNA/ml plasma and normal CD4/CD8 ratios after a median of 18 months of HAART had a single STI. CTL responses were measured by IFN-g ELIspot using HLA restricted peptides. The viral load set point upon TI remained unchanged and was acquired by a median of four weeks following the stop (median two - six weeks).

This viral load increase correlated with CD38 and HLA-DR activation markers on CD4 and CD8 T cells and inversion of the CD4/CD8 ratio. The numbers of CTL in the periphery strongly correlated with the numbers in the lymph nodes (R=0.92, P=0.0001). Lunzen showed that HIV-1 specific CTL in the lymph nodes are stronger and broader than in the peripheral blood. In conclusion it was suggested that the HIV-1 specific CTL that emerge in the periphery following STI are expanded from those that persist in the lymph nodes during HAART, which would thus not effect viral set point. (TuOrA1180)

All references to the XIV International AIDS Conference, Barcelona, 7-12 July.


CONFERENCE REPORT
THE XI INTERNATIONAL HIV DRUG RESISTANCE WORKSHOP
2-5 July, 2002. Seville

Short resistance reports from Seville
Simon Collins, HIV i-Base

CX/R5 phenotype and replicative capacity of resistant virus

As research progresses on entry inhibitors, biological phenotype (CCR5/CXCR4) may become increasingly important within treatment choices. This study of 28 HIV-infected patients failing ARV treatment found that although viral load levels were similar, people with R5 phenotype had a higher number of resistant mutations. The six isolates with >14 mutations in this group were all R5, although the R5 group retained higher CD4 counts and significantly lower replicative capacity of their HIV isolates (p=0.008).

All isolates had reduced replicative capacity compared to wild type, with lowest replicative capacity when >5 mutations were present. Highest replicative capacity was retained when NNRTI-associated K103N and Y181C mutations were present.

As expected, higher HIV isolation was reported in patients who maintained high replicative capacity.

Superinfection shown in vitro and in model

Chakraborty and colleagues reported two studies that reinforced the plausibility of superinfection.

In vitro experiments involved infection and reinfection of peripheral blood mononuclear cells (PBMCs) with wild type (WT) and drug resistant (R) virus in the presence and absence of drug. In the absence of drug, WT virus out-competed the R virus and did not allow reinfection with the less fit strain. In the presence of 3TC, the R virus was more fit than WT virus, was able to super infect WT virus and prevented super infection from WT virus.

Analysis of five replicates of three different HIV-1 superinfections in SCID-hu Thy/Liv mice, which had been infected and then superinfected seven days later, showed reinfection on one viral combination set. This provided evidence that an animal model can be used to study superinfection.

The group have also been following 15 seropositive couples, independently infected and not practising safe sex from two-four years with longitudinal samples taken at a minimum six monthly intervals. No evidence of superinfection has been found in follow up so far, though details of ARV treatment were not included in the abstract.

Ref: Chakraborty et al - Evaluating HIV-1 superinfection in cell culture, the SCID-hu Thy/Liv model and HIV-infected individuals with high risk of exposure to the virus. Seville Abstract 55. Antiviral Therapy 2002; 7:S47.

Theoretical rationale for sequential monotherapy in salvage therapy

Andrew Phillips from the Royal Free Centre for HIV Medicine London presented a theoretical basis for treating multiple drug resistance based on a new paradigm. Continued use of 3TC despite high-level resistance due to the key M184V mutation is recognised to provide benefit (up to –0.4 log) due to reduced replicative competence and several studies at the resistance meeting looked at this for other drugs.

Given that resistant virus is less fit compared to wild type they developed a model for rotating drugs (mono, dual, triple therapy) on a daily or weekly basis, The model relying on the fact that it takes a few days for the virus which can replicate best on any one day to grow in number. Although combinations of drugs were not included, apparent antagonisms between particular drug mutations might be particularly useful to exploit

See overview of this study on page 25-26 of this HTB.


Phenotypic and genotypic predictors of response to tenofovir

Two studies at the workshop and an oral presentation at Barcelona evaluated predictors of response to the recently approved nucleotide analogue tenofovir DF (TDF) from results of previous studies in treatment experienced patients.

Masquelier and colleagues reported on genotypic determinant of response to tenofovir in a sub-group of 191 patients treatment experienced patients enrolled in the French ATU (expanded access programme). [1] Baseline genotype on stable therapy and change in viral load after adding tenofovir for three months were correlated to evaluate the role of each RT mutation and to construct a mutation score validated by bootstrap sampling.

Baseline viral load was 4.9 log 10 copies/ml (3.6-6.3) and mean decrease at month 3 was 0.9 log copies/ml (range –3.2 - +1.8).

RT mutations individually associated with a poorer response were M41L, E44D, D67N, T69D/N/S, V118I, L210W and T215Y/F. The number of these mutations (excluding V118I) formed the basis for a TDF mutation score corresponding to the most significant p value. In their analysis, a score of <3 predicted absence of resistance, 3-4 possible resistance, and >4 resistance. Corresponding reductions in viral load for each group was –1.3 ±1.1 log, -0.8±1.1 log and –0.4 ±0.9 log copies/ml respectively.

The score was found significant in all bootstrap samples, although multivariate analysis was not presented to validate these results. Also, it is important to remember that unlike the Gilead 907 Study, patients in this EAP programme may have changed or added other drugs at the same time as adding TDF. Viral load responses were not solely related to TDF, and the analysis for the contributory role of TDF is not currently available.

Gilead’s analysis of the role of genotypic mutations from virology sub studies of their 902 and 907 studies (n=332 genotypes) reported two mutational pathways. Pathway 41-210-215 was associated with higher TDF resistance particularly of additional TAMS were present. Although K67R is associated with resistance and limited response addition mutations in the presence of the 67-70-219 pathway did not produce further resistance. Viral load reductions for patients without thymidine analogue mutations (TAMS), with 1-2 TAMS and with ≥3 TAMS without M41L or L210W of –0.67 (n=61) of –0.8 (n=97) and -0.66 (n=88) and respectively. Patients with ≥ 3TAMS including M41L or L210W had responses of –0.21 log (n=86). [2]

Phenotypic resistance tests are increasingly used when genotype results are unclear and as an additional tool in heavily treated patients. These tests rely on determining individual sensitivity cut-offs for each drug, and these cut-offs frequently

...
require revision and often vary depending on the assay being used.

The Virco Antivirogram previously established that a cut-off of fourfold for tenofovir was equivalent to 24-week reduction in RNA viral load of only −0.24 log copies/ml.

In this study Miller and colleagues from Gilead Sciences, looked at phenotypic cut-offs, using ViroLogic PhenoSense assay from 112 randomly selected patient from the Gilead 907 study which added TDF for 24 weeks to a failing background therapy (viral load >500 copies/ml). [3]

Mean baseline susceptibility was 1.55-fold from wild-type control (range 0.3-13) and mean week 24 response was 0-63 log copies/ml (range −2.03 - +1.16). Categorical response variables were created corresponding to ≥3, ≥4 and ≥5 log average reductions in viral load and well as for nadir ≥5log reduction from baseline. Bootstrap analysis (n=3000) revealed two splits for susceptibility at values of 4.0 and 1.1.

The biological cut-off for the PhenoSense assay is 1.4-fold (ie 99% of wild-type virus falls within 1.4-fold sensitivity of the drug sensitive reference virus). Using cut-offs of ≤1.4-fold, 1.4-4-fold and >4-fold showed median viral load responses of −0.77 (n=78), -0.37 (n=26) and −0.06 (n=8) respectively.

**COMMENT**

*Given the range of results even with mutation score >4, some patients may still benefit from TDF. However, phenotypic resistance >4-fold does appear to predict lack of clinical response.*

References:

2. M.D. Miller et al - Expanded response analyses of tenofovir DF Therapy by Baseline Resistance Genotype and Phenotype - Barcelona [ThOrB1390]

**Importance of intermediate mutations at 215 in treatment naive patients**

Two studies provided conflicting conclusions on the importance of less frequent substitutions at codon 215 (‘revertant’ C, D, E, N, A, V and S substitutions).

Riva and colleagues from the Italian ICoNA study looked at 405 treatment naive individuals who had a genotypic test prior to starting a thymidine analogue combination. Virological failure was defined as time to the first of two consecutive viral load tests after >24 weeks therapy. Thirteen (3%) patients were found to have 215 variants at baseline (D=6, c=1, E=2, N=1, A=1, V=1 and S=1) and two patients (0.5%) additionally had the more significant T215Y mutation. Treatment was started with 2RTIs and either a PI or NNRTI in over 90% cases, with AZT used in approximately 75% and d4T in 25% regimens.

Multivariate Cox regression analysis, including variables pre-HAART viral load, use of Invirase as only PI, use of AZT, number of prior RT and PI mutations, and time from seroconversion to date of test showed that patients carrying 215 substitutions had an increased risk of virological failure compared to patient without these mutations (adjusted RH=2.44, 95% CI 1.01-5.89, p=0.04). 9/13 patients with 215 substitutions experienced virological failure. Resistance test at time of failure in five of these patients showed reversion to T215Y in three cases.

Lanier and colleagues from GlaxoSmithKline looked retrospectively at baseline genotypes from 574 treatment naive patients from three studies using AZT/3TC with either indinavir, abacavir or efavirenz. Genotypes at failure (confirmed viral load >400 copies/ml) were available for >90% of patients.

2.8% of patients showed baseline mutations at 215 D/C/S (n=8, 4, 4 respectively). M41L was detected simultaneously in 5 cases and L210W in one. 6/16 patients with mutations at baseline later failed virologically, and in three cases the dominant species became 215Y. The small numbers of cases didn’t allow for an analysis of a preferential regimen, and the continued detection of revertant mutations was not always associated with treatment failure.

References:


Genotypic resistance to nelfinavir detected 4 months prior to viral rebound >500 copies

Descamps and colleagues reported on 16/21 antiretroviral naive patients failing first line nelfinavir containing regimens with successfully amplified protease genotypic results. Failure was defined as a viral load >500 copies/ml over the first year of follow up and genotypic testing (ViroSeq) with additional nested PCR performed at -4 month (S1) and -2 month (S2) prior to failure and time of rebound (baseline).

In 8/16 patients, wild type virus was present at all three time points. In the other eight patients mutations were detected prior to rebound at S1 or S2. In two cases resistance at rebound matched the earlier samples but major or minor differences were detected in the remaining six indicating minor viral species can evolve with some drugs even at levels <500 copies/ml. At time of rebound 3/8 remained wild type, and 5/8 harboured D30N, associated with N88D or M46I+V77I in two cases.

Amplification of RT gene in 15 patients revealed no RT mutations in seven patients receiving ddI/d4T/nelfinavir. M184V mutation was detected at S1 or S2 in 8/9 evaluable patients receiving 3TC-containing regimens.

Without full details on more sensitive levels of suppression - and the treatment goal for all naive patients is now recognised as suppression to <50 copies/ml - it is difficult to draw conclusions from this study. However it should reinforce the concern that suppression to only <500 carries high risk of subsequent viral rebound and evolution of drug resistance while still <500 copies/ml


Clinical use of ddI in patients with M184V mutation, with and without 3TC

In vitro data have suggested that M184V may reduce the efficacy of ddI. Several studies suggested that this should not be a concern in clinical practice, whether or not 3TC is included in the subsequent regimen.

Pozniak and colleagues performed a retrospective analysis of the proportion of patients achieving viral load <400 copies and the average area under the curve (AUC) viral load response in 281 patients followed for at least 48 weeks who switched to ddI-containing regimens in a cohort at the Chelsea and Westminster Hospital in London. [1] Baseline characteristics and univariate analysis of changes in viral load were performed using Wilcoxon rank sum test. Multivariate analyses were performed using the Van Elteren test. Additional variables included baseline RT mutations, previous PI and NNRTI use and whether 3TC was used in the subsequent regimen.

Patients with the M184V mutation at treatment switch (105/281) had greater median fold change in phenotypic susceptibility to ddI than patients without 184 (2.2 vs. 1.2-fold, p<0.001). However in both univariate and multivariate analyses, median change in viral load and percentage of patients achieving <400 copies was similar irrespective of 184 at baseline. Additionally patients with 184 at baseline showed a significantly better AUC response if treated with ddI-containing regimens compared to those who didn’t use ddI (p<0.03).

A second study from Eron and colleagues looked at treatment response in patients from ACTG 307. This double-blinded eight-week study compared ddI monotherapy to using ddI with two different doses of hydroxyurea in 134 treatment naive and experienced patients. Previous treatment was discontinued 14 days prior to the study. [2]

16/24 3TC-experienced patients had baseline genotype, 13 of which included 184V. Median baseline viral load were 4.2 (IQR 3.8-5.1), 4.6 (4.2-5.0) and 4.6 (4.3-4.9) in the 3TC-naive, 3TC experienced (without 184) and 3TC-experienced with 184 arms. Decreases in HIV RNA at week 8 were 1.81 (n=52), 1.42 (n=24) and 1.42 (n=13) respectively. In analysis by treatment arm, decreases of 0.89 (19), 0.77 (7) and 0.77 (4) were recorded for patients receiving ddI alone and 1.94 (19), 1.69 (7) and 1.63 (9) for patients receiving ddI/HU.

Aside from showing a substantial benefit from hydroxyurea, and despite slightly higher decreases in viral load in 3TC-naive individuals, previous 3TC therapy appeared to have minimal short-term effect on antiviral activity of ddI, with or without hydroxyurea.

Winters and colleagues looked at the effect of M184V on the response to ddI in 63 nucleoside experienced (AZT/3TC or AZT/3TC/ddC) patients who rolled over to ddI/d4T plus nelfinavir, indinavir or nelfinavir + indinavir in the ACTG 364 Study. Forty one additional patients on AZT/3TC/ddI were randomised to d4T/ddI or d4T/3TC plus either nelfinavir, indinavir or nelfinavir + indinavir. [3]

Although reporting in multivariate analyses that M184V did not significantly contribute to ddI resistance in vivo, the overlapping use of other nucleosides, complexity of switched treatments. Low numbers of patients and a high definition of virological failure at >2000 copies/ml probably limits the practical results from this study.

References:
1. Pozniak et al - Influence of M184V mutation on virological outcome of HAART with or without didanosine. Seville. Abstract 152. Antiviral Therapy
New anti-HIV compounds discussed at the Seville HIV Drug Resistance Workshop and the Barcelona World AIDS Conference

Mike Youle MD, for HIVandHepatitis.com

The sun-drenched heart of Spain in Seville provided a pleasant setting for the XI International HIV Drug Resistance Workshop. Approximately 250 delegates met to discuss the hot topics in resistance.

As usual, they faced an ever increasing range of agents to study that now spans more areas of the virus life-cycle and a wider selection of tests with which to evaluate resistance to these compounds.

Please note that unless otherwise indicated, all references are to the Programme and Abstracts of the XI International HIV Drug Resistance Workshop, July 2-5, 2002, Seville, Spain OR to the XIV International AIDS Conference, July 7-12, 2002, Barcelona, Spain. The Seville Workshop abstracts are published in Antiviral Therapy Volume 7(2) and are available on-line.

Considering that we have not had a new class of compounds to use for more than six years, the advent of receptor blockers, fusion inhibitors and the integrase inhibitors are great news. Let us hope that physicians have learnt not to burn through these new opportunities without considering the implications of just adding the next new drug to a failing regimen.

Daria Hazuda and Steve Young revealed tantalizing results of their work with the Merck integrase inhibitors [Seville Abs 1, 2, Abs TuPeA4371]. They have modified the diketobutanoic acids structures that had showed efficacy in vitro to produce a series of new compounds with increased activity including against multi-HIV resistant (MDR) strains of HIV and which shows synergy with other available agents. In a macaque model drops of 1-3 log were seen in viral load and the lead compound, L870810, has good bioavailability and a half-life in macaques of 8.6 hours. Mutation at positions 153 and 155 lead to a 9-11 fold reduction in activity but this drug seems to work at much lower (nanomolar concentrations) compared to the Shionogi-GSK compound S1360 presented at the 2002 Retroviruses and OL meeting in Seattle, WA [1].

At the XIV International AIDS Conference in Barcelona, further data on the oral administration of the latter compound was reported [Abs TuPeB4431, TuPeB4436]. Twenty-four uninfected volunteers were given escalating multiple doses of S1360 of 500mg, 1000mg and -2000mg twice daily under fed conditions. The drug appeared to be well absorbed with the maximum drug level achieved at 2-3 hours without the drug accumulating over time. It was heavily protein bound which might result in problems for the availability of the active drug but tolerability in these subjects seemed good with headache and nightmares being the only consistent side effects reported.

Next old kid on the block was MIV-310 that last saw the light of day in the early 1990’s. This agent is a fluorothymidine related to zidovudine, which is being re-evaluated by Medivir. It appears to work against MDR but has problems with leucopenia in high doses. In this study conducted in Paris, the drug at a 7.5mg dose was used as an add-on agent in subjects failing virologically between 1-50,000 copies/mL [Seville Abs 3]. The overall median viral load drop was 1.13log10 [n=15] with a lower viral load drop in subjects who also received stavudine. This raises the question as to if there may be a similar inhibitory action as seen with zidovudine and stavudine. During the four weeks of therapy no resistance mutations emerged and although some concerns exist regarding the safety profile of the drug this is an exciting rebirth that should be watched with interest.

Rich Colono from BMS next showed updated data on the resistance patterns of atazanavir [Seville Abs 4]. It appears that when the IS0L emerges under the effect of atazanavir [ATZ] in treatment-naïve patients they seem to be more sensitive to the other protease inhibitors. So if ATZ is used as a first-line agent, PI patients should still be sensitive to other agents, the same story the D30N for nelfinavir. In PI-experienced patients who received ATZ with saquinavir they did not see patients developing the IS0L but it will now be studied in patients receiving ATZ without saquinavir. Using the ViroLogic replication assay, this virus carrying the IS0L did not replicate as easily. At Barcelona in the late breaker session Rob Murphy of Northwestern University Chicago presented data on subjects who completed AI424-008 and then switched from nelfinavir to atazanavir [LbPeB9013].

In the 364 patients a significant reduction in fasted total and LDL cholesterol as well as triglycerides was seen over 12 weeks, once again suggesting that this new protease inhibitor may have significant benefits over the currently available agents.

Marie-Pierre Bethune then updated the story on the Tibotec (now Johnson and Johnson) protease inhibitor TMC 114 [Seville Abs 5]. This agent that appears to be highly active against most currently available isolates was entered into a serial passage experiment. This experiment resulted in no detectable selection of resistance even after 260 days at 100nm compared to selection for resistance to nelfinavir after 20, amprenavir by 30 days, days and lopinavir by 90 days. Finally, at the higher doses viruses were isolated harboring R41T and K70E mutations but with a fold change of only 10. These viruses were sensitive to other PI’s except saquinavir, suggesting little cross-resistance for this drug with a high genetic barrier to resistance.

Another offering from Bristol Myers Squib was BMS-806, their novel HIV-entry inhibitor presented by Ping-Fan Lin [Seville...
New antiretroviral drug data presented in Barcelona

Barcelona was a huge gathering of the world leaders in all fields of HIV, but there was little showcasing of really novel antiretrovirals other than the fusion inhibitor T-20 and some new data on atazanavir. Much of the work seen at Seville was rehearsed (referenced above) and there were a few new agents presented.

The data on enfuvitide (T-20) included presentations of the TORO 1 and TORO2 studies [Abs LbOr19a, LbOr19b] that are reviewed elsewhere. Although T-20 is an injected agent, patient acceptability, at least in the short term, seemed high with over 75% of subjects finding little or no limitation to their daily activities [Abs TuPeB4480]. How much of this was driven by the fact that this data was at eight weeks and in the setting of good surrogate market outcomes is unclear. When injection sites of the abdomen, arm and leg were compared in 12 subjects in a crossover manner it appeared that the thigh absorbed T-20 better than the abdomen or the arm but that the difference was not statistically significant [AbsTuPeB4542].

On the first day, data on a new purine analogue reverse transcriptase inhibitor called SPD 756 (BCH-13520) was shown [Abs MoPeA3008]. This agent, although a weak inhibitor in the test tube, has been modified by deamination to produce SPD-761 TP, a potent agent that has the advantage of activity against multi-drug resistant strains of HIV which is now being moved into later phase development by Shire Biochem of Canada.

Further compounds tested in vitro included a novel Tat inhibitor/antagonist, NeoR [Abs MoPeA3001], and a betulinic acid derivative PA-457 coming out of University of North Carolina, Chapel Hill and Panacos Pharmaceuticals [Abs MoPeA3030]. This appears to have a direct effect on virion assembly whilst being orally bioavailable and effective against R5 and X viruses.

This research group also showed data on another unusual drug with unknown site of action, PA-344B, which is under investigation and has activity against drug resistant strains of HIV [Abs TuPeB4435]. A novel combination approach to integrase inhibition used the strand transfer blocking diketoacids with L-chioric acid that appears to not only inhibit integrase activity but to act as a partial entry blockers producing a synergistic effect  [Abs MoPeA3021].

Another group from Progenics has humanized an anti-R5 monoclonal antibody, PRO 140 that appears to block HIV-1entry without interfering with the chemokine receptor activity of R5 and has moved it into phase 1 studies [Abs TuPeA4363]. Following a long campaign by some researchers to suggest aspirin has a beneficial effect against HIV, Candida Pereira and co-workers from Amsterdam presented data on an aspirin-like compound that had activity on reverse transcriptase that was synergistic with other RT inhibitors [Abs LbPp2207].

At Barcelona a poster presentation described the surrogate marker outcomes and tolerability of the Phase IIA study of the other Tibotec compound, TMC-125, in subjects with NNRTI resistant strains [Abs TuPeB4438]. Sixteen subjects were given 900 mg TMC-125 twice daily instead of the failing NNRTI but continued on the same background therapy for seven days before constructing their next regimen. The median baseline CD4 count before switching to TMC-125 was 389 cells/mL and viral load 10,700 copies. Before commencing TMC-125 resistance to TMC-125 was 0.5-8 fold. In this study diarrhoea and headache were seen in around 25% of patients and the median viral load drop was –0.86 log (range from -1.95 to +0.09) by day 8.

In the late breaker session two posters examined the antiviral activity and action in conjunction with structured treatment interruptions of Ampligen, a double stranded DNA, poly:C12U [Abs LbBe9010, LbBe9011]. This agent given intravenously appeared to achieve a modest drop in HIV RNA or 0.25log10copies/mL after 24 weeks in eight patients.

In the second study that comprised adding poly:C12U [Ampligen] to HAART prior to a structured treatment interruption there was a significantly delayed period, 25+ weeks [n=6] versus a median of seven weeks [n=4] to a persistent viral rebound of >5,000copies/mL in the group randomised to the active therapy. Although these studies are in small numbers they provide some suggestion that these antiviral biologic response modifying RNA molecules may be yet another approach to HIV therapy.

Overall a rather good crop of new agents, which if adequately watered and nurtured, could turn into a bumper harvest of treatment options in the next few years.


Copyright 2002 by HIV and Hepatitis.com. All Rights Reserved.
Review of phenotypic resistance testing data presented at the XI International HIV Drug Resistance Workshop

By Mike Youle MD, for HIVandHepatitis.com

The measurement of resistance to HIV has sped on in leaps and bounds, and with each new conference comes technologic improvements, novel technologies or modification of existing ones as well as more information on how to maximize the utility of these tests. At the XI International HIV Drug Resistance Workshop (July 2-5, 2002, Seville, Spain) there was a wide application of phenotypic resistance tests and the derived replication capacity measure, some of which are discussed below.

Please note that unless otherwise indicated, all references are to the Program and Abstracts of the XI International HIV Drug Resistance Workshop, July 2-5, 2002, Seville, Spain. All abstracts are published in Antiviral Therapy Volume 7(2) and are available on-line.

Replication capacity

A novel replication capacity assay has been developed as a modification of the PhenoSense phenotypic resistance assay in which the capacity to replicate of the patient viral strain is expressed as a percent of that of a wild-type reference virus (NL4-3).

In a prospective study of phenotypic susceptibility testing (CCTG 575), 97 of 207 patients who failed to suppress HIV RNA at month 6, showed a significant linear correlation between lower RC and greater month 6 HIV RNA reduction (r=0.34, P=0.001) [1].

Although the baseline HIV RNA was the same in each group, patients with lower RC (<35%, n=49) had a mean HIV RNA change of -0.54 log10 at month 6 compared to +0.08 for those with higher RC (n=48, p=0.0003). In a multivariate model with RC, baseline HIV RNA, CD4, and the number of NRTI, PI and NNRTI to which the virus was susceptible, only the baseline HIV RNA (p=0.004) and RC (p=0.0002) were independent predictors of month 6 HIV RNA change.

In another study clinical and laboratory data from 12 studies of RC in over 800 clinical viral isolates (N>500 patients) were evaluated [2].

Data across studies were linked to define a continuous model of viral/clinical evolution during the course of HIV infection and antiretroviral treatment. During early HIV infection, wild-type virus, spanning a broad range of RC (<10% to >100%) usually predominates. Viruses with lower RC during early infection are associated with higher CD4 cell counts, suggesting a slower rate of immune depletion.

Upon initiation of therapy, RC effects appear to be obscured by the magnitude of the antiviral drug effects. After onset of treatment failure associated with emergence of drug resistance, the RC often declines precipitously, especially in the setting of protease inhibitor resistance but less so in the face of isolated NRTI or NNRTI resistance; and the RC drop is directly correlated with the magnitude of viral load suppression and CD4 cell increase from the pre-treatment baseline.

During prolonged virologic failure, RC tends to remain relatively stable despite a slow, progressive increase in drug resistance and viral load. The presence of virus with higher RC is associated with CD4 cell decline, and a lower RC with CD4 increases.

If treatment is interrupted, wild-type virus with higher RC usually re-emerges over 2-12 weeks, in association with abrupt increases in viral load and declines in CD4 cell counts toward pre-treatment baselines.

Transmission

There remain many unresolved issues concerning the transmission of HIV-resistance at primary infection. The ViroLogic PhenoSense HIV assay was used to assess the prevalence of transmitted drug resistance across three study periods: A=1995-1998 (n=264), B=1999-May, 2000 (n=123), and C=June 2000-March 2002 (n=122) [3].

Baseline characteristics did not differ over time and the proportion of subjects with an IC50 >10 times the reference virus (NL4-3) to one or more ARV drugs did not change significantly between period B and C (12.2% vs. 6.6%, p=0.13). This compared to an increase from A and B (3.4% vs. 12.2%, p=0.001).

Resistance to non-nucleoside RTI (NNRTI) from period B to period C (7.3% vs. 6.6%, p=1.00) was stable. However resistance to nucleoside RT inhibitors (NRTI) (5.7% to 0.8%, p=0.06), PI’s (8.1% to 0%, p=0.002) and multi-drug resistance (an IC50 >10 fold to drugs in 2 or more classes) decreased significantly between these same study periods (6.5% to 0.8%, p=0.04).

To assess the effect of transmitted drug resistance 130 persons recently infected with HIV-1 were identified in the Options Project, a study of primary HIV-1 infection based in San Francisco [4].

Drug resistance was assessed both phenotypically (PhenoSense HIV) and genotypically (TruGene HIV). CD4 T-cell counts were significantly higher in subjects with genotypic evidence of drug resistance (P=0.02) or decreased replication capacity (P=0.01). These associations persisted after controlling for duration of infection.
RC was significantly lower in subjects with genotypic PI resistance compared with wild-type (median RC 24% vs. 41%; P=0.04) and ranged widely from 1% to 113%. Hypersusceptibility to protease inhibitors (defined as IC50 fold change < 0.4 for any PI), was observed in 17.6% and correlated with lower replication capacity (eg: IDV IC50 fold change vs RC; Rho 0.52; P= <0.001).

The wide variation in replication capacity of recombinant viruses containing PR-RT segments derived from recently transmitted HIV-1 may reflect the diversity of quasispecies capable of establishing new infections, or bottlenecks in the virus population as a result of poorly understood selective pressures exerted during virus transmission.

**Antiretroviral resistance**

To assess the utility of phenotyping resistance to protease inhibitors PR genotype (GT) and phenotype (PT) for 1418 patient samples with at least one primary PR mutation or one PI with reduced susceptibility (fold change [FC]>2) were analyzed [5]. Samples were classified as LPV resistant by GT (GT-R) if six or more LPV mutations were present, and by PT (PT-R) if the FC was over 10. APV GT-R was defined as presence of any of primary APV mutation, and PT-R was defined as FC > 2.5.

Using a published LPV algorithm, 182 samples classified as GT-S (13%) actually tested PT-R. A comparison of the prevalence of PR mutations in the discordant GT-S/PT-R samples and the concordant GT-S/PT-S samples (n=489) identified several new mutations that are significantly associated with LPV PT-R. This finding has implications for the use of LPV-based salvage therapy after failure of APV-based regimens, or vice versa.

In a further analysis of amprenavir susceptibility data from >3000 clinical samples displaying evidence of reduced PI susceptibility by phenotype (PT) or genotype (GT) were examined to establish a clinical cut-off for APV resistance [6]. Since this is currently unknown, a conservative estimate of 2.5-fold increase in IC50 was used to define samples with reduced APV susceptibility (PT-R).

Samples were defined as resistant by GT (GT-R) if any of the following mutations were present: V32I, I50V, I54L or M, or I84V. One quarter of the initial genotypic interpretations were discordant with the observed phenotypic results. Data analysis identified novel combinations of these and other mutations that added significant predictive information, including L33F/V82A, V82F/L90M, M46I/I47V, and M46I/V82F.

It would seem that reduced susceptibility to APV can develop via genetic pathways that do not include APV-selected mutation and that using APV PT data to define mutations associated with cross-resistance leads to an improved ability to predict reduced susceptibility from genotypic data.

To assess the impact of IDV resistance on responses to RTV-enhanced regimens in patients who had virologic failure on multiple protease inhibitors 173 patients were identified from three observational cohorts and one prospective clinical study on a variety of indinavir/ritonavir regimens [7].

A meta-analysis of these populations was performed to assess the relationship between baseline IDV fold change (PhenoSense assay) and subsequent virologic responses to the IDV-RTV regimen. Phenotypic susceptibility at baseline correlated inversely with clinical response to IDV-RTV based therapy. The clinical cutoff for IDV-RTV 800/200 is at least five to ten fold.

More sophisticated statistical analyses (regression and/or CART) will be required to define a precise clinical cutoff.

To further describe phenotypic (PT) and genotypic (GT) patterns associated with (atazanavir) ATV resistance PT (PhenoSenseTM) and GT (GeneSeqTM) evaluations were performed on baseline and post-treatment isolates from 76 patients treated with ATV and classified as treatment failures in studies AI424-007, -008 and -009 [8].

Seventeen of the post-treatment (24 to 104 wk) isolates from patients designated as treatment failures displayed decreased susceptibilities to ATV ranging from five to 141-fold. Recombinant viruses containing I50L and the I50L/A71V combination displayed decreased susceptibility to ATV and were significantly growth impaired. PT and GT analysis of isolates from patients treated with regimens containing ATV suggest that the emergence of the amino acid substitutions I50L and A71V in treatment naïve patients may result in selective resistance to ATV.

With the Antivirogram, a tenofovir phenotypic cut-off of four-fold was previously established and this corresponded to a week 24 HIV RNA response to TDF therapy of only −0.24 log10 copies/mL [9].

Using study 907 a phase III study of TDF when added to stable background antiretroviral therapy in treatment-experienced patients with extensive resistance mutations. Baseline HIV phenotypes were obtained for 112 randomly selected patients with >500 HIV RNA copies/mL at baseline and outcomes assessed at week 24 to establish clinical cut-off using the PhenoSense HIV assay.

The mean week 24 response was −0.63 log10 copies/mL (range −2.03 to +1.16) and using categorical response variables the biological/assay cut-off for tenofovir was 1.4-fold, i.e. 99% of wild-type viruses from treatment-naïve patients fall within 1.4-fold of the drug sensitive reference virus. There appeared to be two clinical phenotypic cut-offs for tenofovir DF in this assay,
with the 1.4-fold level corresponding to a reduced response to TDF therapy (23% of patients fell above this cutoff) and a second cut-off of four-fold corresponding to no clinically significant response (7% of patients).

In ACTG 364, a randomized clinical trial in highly nucleoside experienced subjects, 131 subjects were treated with NFV as their first PI[10]. Virologic failure (VF) occurred in 48 (37%) NFV-treated subjects and 38/66 (58%) and 10/64 (16%) subjects randomized to the NFV+nRTIs and NFV+EFV+nRTIs arms, respectively.

Genotype (Stanford ABI) and phenotype were retrospectively determined from plasma at study entry (n=86) and initial failure (n=39 genotype, n=32) both or continued failure (n=22). Failure was frequently associated with reduced susceptibility to NFV and the emergence of ‘secondary’ mutations.

Continued NFV use after VF selected for progressively increasing NFV resistance in a majority of subjects. Cross-resistance to other protease inhibitors, however, was infrequent and low-level in these NFV-treated VFs.

A Spanish group presented another study, which compared phenotype with virtual phenotype. They randomised 300 subjects to one or the other and showed that the virtual phenotype gave a slightly better ability to detect resistance using the virtual phenotype with some drugs [11]. However this may have been related to the choice of cut-off compared to the constantly changing algorithm of the virtual phenotype. Overall no significant differences in outcome were seen.

Treatment selection patterns appear to be influenced by availability of information. In the CPCRA 064 study of structured treatment interruption followed by a salvage regimen 245 patients were enrolled and their physicians were asked to decide on a salvage regimen based on initially genotype only and then later in the STI on genotype plus phenotype (VIRCO) [12]. Seventy two percent changed their assessment when the additional information was available.

A new class of compounds requires a new set of resistance assays and Bristol Myers Squibb Research Institute has developed an entry inhibitor assay to parallel their development program of BMS-806 [13]. It is based on generation of transcriptionally active fragments of HIV envelope and a viral envelope mediated fusion assay. This results in a rapid (around five days) relatively simple assay for this new group of drugs.

In summary, there was a plethora of information on phenotypic assays of various types at the Seville Resistance Meeting, which moved the field forward to allow better monitoring, and evaluation of HIV drug resistance.

References:

Unless otherwise indicated, all references are to the Program and Abstracts of the XI International HIV Drug Resistance Workshop. July 2-5, 2002. Seville, Spain. All abstracts are published in Antiviral Therapy Volume 7(2) and are available on-line:

http://www.mediscover.net/journals.cfm


2. NS Hellmann, T Winr, M Bates, S Deeks et al. Modeling the Effect of HIV Replication Capacity on Treatment Outcomes. Seville Abs 63


4. RM Grant, JD Barbour, T Winr et al. Transmission of Drug Resistant HIV-1 Exhibiting Lower Replication Capacity is Associated with Higher CD4 Cell Counts. Seville Abs 46

5. NT Parkin, C Chappey, and CJ Petropoulos. Mutations in HIV-1 Protease Associated with Resistance to Amprenavir Contribute towards Phenotypic Resistance to Lopinavir. Seville Abs 24


7. J. Szumiloski, H. Wilson, E. Jensen et al. Relationship between Phenotypic Susceptibility to Indinavir and Virologic Response to Indinavir-Ritonavir-Containing Regimens Following Failure of a Previous Protease Inhibitor. Seville Abs 155

8. RJ Colomao, J Friborg, RE Rose, et al. Identification of Amino Acid Substitutions Correlated with Reduced Atazanavir Susceptibility in Patients Treated with Atazanavir Containing Regimens. Seville Abs 4


10. D Katzenstein, Gerald Downey, Ronald Bosch et al. Evolution of Protease Phenotype and Genotype Changes at Initial and Continued Virologic Failure among Nucleoside-Experienced Subjects Receiving Nelfinavir (NFV) in ACTG 364. Seville Abs 144

11. M Perez-Elias, I Garcia-Arata, S Moreno et al. Baseline Testing information given by a real phenotype (real Ph) or a Virtual Phenotype (Virtual Ph) test in a Randomised Study (RealVirfen study):influence in final outcome. Seville Abs 109


ANTIRETROVIRALS

Trial supports lopinavir/ritonavir as first-line therapy in HIV infection
A combination of lopinavir and ritonavir is well tolerated and has antiviral activity that is superior to nelfinavir-containing regimens in the initial treatment of HIV infection, a study in the New England Journal of Medicine confirms.

Lopinavir is a newly developed peptidomimetic protease inhibitor that when formulated with low-dose ritonavir, a cytochrome p450 3A4 enzyme inhibitor, has enhanced pharmacokinetic profile. The combination yields mean trough plasma lopinavir concentrations that are at least 75 times as high as that needed to inhibit replication of wild-type HIV by 50%.

The clinical efficacy of the combination had been demonstrated in a previous Phase II study, in which lopinavir/ritonavir plus stavudine and lamivudine was given to antiretroviral-naive HIV-infected patients. On the basis of the trial’s favourable outcome, Sharon Walmsley and colleagues conducted a double-blind trial to compare the safety and efficacy of lopinavir/ritonavir with that of nelfinavir.

In all, 653 HIV-infected patients who had not previously received antiretroviral therapy for more than 14 days were randomly assigned to receive either lopinavir/ritonavir plus nelfinavir placebo, or nelfinavir plus lopinavir/ritonavir placebo. All patients also received open-label stavudine and lamivudine.

At 48 weeks, 75% of patients in the lopinavir/ritonavir group had reached the primary endpoint of HIV RNA <400 copies/ml, compared with 63% in the nelfinavir group. This difference reached statistical significance (\(P<0.001\)).

Patients receiving the lopinavir/ritonavir combination also had a longer time to loss of virologic response than those receiving nelfinavir, with a hazard ratio of 2.0 (\(P<0.001\)). The proportion of patients with a sustained virological response through the 48-week study period was 84% in the lopinavir/ritonavir group versus 66% in the nelfinavir group.

Significantly, no resistance mutations in HIV protease were reported during the study period in patients with >400 copies HIV RNA/ml taking lopinavir/ritonavir. In the nelfinavir group, such mutations occurred in 33% of patients (\(P<0.001\)). Furthermore, the combination regimen was well tolerated, with fewer treatment-related discontinuations than with nelfinavir (3.4% versus 3.7%).

‘The findings from this trial show the benefits of therapy with lopinavir/ritonavir, as demonstrated by its superior antiviral activity in comparison with that of nelfinavir and its continued tolerability and high barrier to resistance,’ Walmsley et al. conclude.

‘These characteristics suggest an important role for lopinavir/ritonavir as an initial protease inhibitor-based treatment for HIV infection.’


Source: www.mediscover.net

Ritonavir has anti-neoplastic effects independent of HIV inhibition
In vitro and in vivo data show that the HIV protease inhibitor ritonavir decreases production of factors that contribute to tumor neovascularization and the development of Kaposi sarcoma (KS).

“We found that ritonavir has significant side effects on immune cell activation,” Dr Frank F Weichold from Morgan State University, Baltimore, told Reuters Health. “It is, in a way, an antiinflammatory [agent]. So ritonavir is not only an antiviral, but also an immune [system] modulator,” he explained. Dr Weichold and colleagues treated KS cells, from a KS cell line, and endothelial cells, from human umbilical veins, with different concentrations of ritonavir over 24 hours.

Compared with untreated cultures, a high concentration of ritonavir (50 µmol/L) reduced the number of viable primary human umbilical vein endothelial cells by approximately 25%, the researchers noted. The researchers also treated human umbilical vein endothelial cells with ritonavir and used ELISA to measure cytokines levels, according to the report in the May 15th issue of Blood. After 48 hours, there were decreases in the levels of interleukin-8, and after 24 hours, there were decreases in tumour necrosis factor-alpha and in vascular endothelial growth factor. These cytokines may all contribute to the development of KS and the perpetuation of KS lesions, Dr Weichold’s team comments.

Ritonavir also inhibited leukocyte adhesion to endothelial cells. This inhibition was dose-dependent, “with less than 60% of adherent cells remaining at concentrations higher than 30 µmol/L.” The research team also found that ritonavir inhibited transcriptional activation of nuclear factor kappa-B, induced by the KS-promoting factor tumour necrosis factor-alpha, the HIV-1 Tat protein, or the human herpesvirus 8 protein ORF74.
“KS-derived cell lines underwent apoptosis in vitro after treatment with ritonavir at concentrations that are obtained in clinical therapy (3 to 15 µM),” they add. In a KS-tumor xenotransplantation mouse model, Dr Weichold’s team also found that ritonavir at 30 mg/kg per day for 15 days slowed the growth of KS-derived cells and significantly inhibited tumour development.

These effects have implications for the use of ritonavir as an antiinflammatory. Also, ritonavir inhibits cellular proteases that might be useful in treating cancer, Dr Weichold said. “We believe that ritonavir might be beneficial in treating solid tumours by inhibiting neovascularization,” he continued. And ritonavir might make leukemia cells more susceptible to other anticancer drugs.


Source: Reuters Health

Antiretroviral use in pregnancy and the risk of an adverse outcome
Polly Clayden, HIV i-Base

Use of antiretroviral therapy during pregnancy for HIV-1 infected women, for benefit to maternal health and to reduce mother to child transmission (MTCT), is now widely recommended. However, there are limited data on complications associated with treatment during pregnancy, and some studies have suggested that combination therapy may increase the risk of premature birth.

A paper published in the June 13th issue of New England Journal of Medicine examined data from a group of women (and their infants) enrolled in seven studies who gave birth during the period 1990 to 1998, to evaluate the risk of premature birth and other adverse outcomes associated with antiretroviral use.

Of the 2123 women using antiretrovirals, 1590 received monotherapy, 396 combination therapy without protease inhibitors and 137 combination therapy including protease inhibitors. A comparitor group of 1143 women did not receive antiretrovirals.

The rate of very premature delivery, defined as delivery at less than 32 weeks, was not significantly different between the groups of treated and untreated women (2% and 1% respectively) unadjusted for CD4 cell count, use or non-use of tobacco, alcohol and street drugs. In addition unadjusted rates among infants of low and very low birth rate, abnormal Apgar scores and stillbirths did not differ between the two groups. Unadjusted rates of premature birth however, defined as delivery at less than 37 weeks, were slightly lower among women treated with antiretrovirals (16% and 17%). Adjusted rates of adverse outcomes however remained similar in both groups.

The authors also found that low maternal viral load and the use of combination therapy during pregnancy are associated with rates of vertical transmission of 2% or less.

Overall the investigators concluded that their “…data provide reassurance that the risks of adverse outcomes of pregnancy that are attributable to antiretroviral therapy are low and likely to be outweighed by the recognised benefits of such therapy during pregnancy.”


METABOLIC TOXICITIES AND SIDE EFFECTS

Triglyceride increase can predict lipodystrophy in HIV patients under highly active antiretroviral therapy
Simon Collins, HIV i-Base

The development of lipodystrophy in HIV patients under highly active antiretroviral therapy (HAART) is an important problem associated with this therapy. Several authors have found inconclusive results when studying the metabolic mechanisms allied with those morphological changes. In order to establish a possible association between changes in serum lipids and lipodystrophy, the authors investigated their evolution in HIV patients receiving HAART.

Of 297 HIV patients receiving HAART, researchers selected 90 subjects in whom adherence to antiretroviral drugs was deemed adequate (more than 95% compliance). Follow-up included baseline and three monthly determinations of serum cholesterol and triglyceride levels. Lipodystrophy was diagnosed when the patient and doctor agreed on the presence of facial
Peripheral neuropathy: New data on risk factors, incidence and association with viral load

Paul Blanchard, HIV i-Base

HIV-associated distal sensory neuropathy (DSP, also known as peripheral neuropathy) is a painful and disabling condition affecting as many as 35% of patients with AIDS. Typical symptoms include pain, paresthesias (usually burning) and numbness usually affecting both feet and occasionally progressing to involve both hands. Neurological testing may reveal reduced or absent ankle reflexes, decreased vibratory sensation in the feet and decreased pain and temperature sensation in a stocking distribution.

Peripheral nerve damage may occur during the process of HIV-infection itself, and also due to toxicities of some antiretrovirals and other drugs used to treat opportunistic infections. Such toxic neuropathies are clinically indistinguishable from HIV-associated DSP. The risk of DSP is known to increase with higher HIV-1 viral load, lower CD4 T-cell counts, advanced disease and increasing age. Antiretroviral therapy impacts some of these risk factors (viral load and CD4 count) and may, therefore, reduce the risk of DSP. Paradoxically, however, if such antiretrovirals are neurotoxic, they may reduce these risk factors yet increase the incidence or severity of DSP. The relationship between such risk factors as viral load and DSP, especially during antiretroviral treatment is therefore an important consideration, particularly if neurotoxic antiretrovirals are being administered. Two recent papers published on DSP help to throw some light on this relationship.

Schifitto and colleagues assessed the incidence of and risk factors for DSP in the Dana cohort of HIV-infected patients [1]. This is a cohort of 272 patients recruited from three study sites in the pre-HAART era (1994 – 95). These subjects were followed for up to 2.5 years with semiannual neurologic, neuropsychological, functional and laboratory assessments. Entry into the cohort was for HIV-infected patients who reported memory or concentration problems, and had a CD4 count less than 200 cells/mL. Patients were also included with CD4 counts < 300 cells/mL if they had evidence of cognitive impairment on neuropsychological testing. It may be assumed, therefore, that these patients were probably at risk for neurologic complications. DSP was diagnosed if subjects had reduced or absent ankle reflexes, decreased or absent vibratory perception at the toes, or decreased pinprick or temperature in a stocking distribution. They were further classified as asymptomatic DSP (ADSP) if despite these findings they had no pain or paraesthesias, or symptomatic DSP (SDSP) if paraesthesias or pain were reported.

At study entry 45% of the subjects were not showing signs of DSP according to the study criteria. ADSP was found in 20%, and SDSP in 35%.

Of the 89 subjects who did not have DSP at study entry and had at least one follow-up visit, 64 (72%) went on to develop DSP. The one year estimated incidence of DSP in these patients being 52%. Of the 128 subjects who did not have SDSP at study entry and who had at least one follow-up visit, 64 (50%) went on to develop SDSP. The one year estimated incidence for the development of SDSP in these patients being 36%.

Baseline variables did not differ at baseline between those subjects with ADSP and those subjects with no DSP. However, SDSP patients tended to be older, had higher D_{2}-microglobulin levels and were neurologically and functionally more impaired than both ADSP patients and no DSP patients.
Time to DSP (ADSP or SDSP) and its association with various risk factors was determined. Only a history of AIDS diagnoses (HR = 1.89) and log CD4 cell count (HR = 0.69) were significantly associated with time to DSP. When time to symptomatic DSP was considered separately, significant associations with time to diagnosis was found for AIDS diagnoses (HR = 2.13) and physical function score >22 (HR = 2.95). Subcategories of the neurological examination and a depression scale rating were also significantly associated with the time to development of SDSP. Sex, DHEA levels, CD4 cell count, presence of ADSP and, interestingly, dideoxynucleoside use within six months of study entry were not significantly associated with time to SDSP. The strongest predictor of SDSP on multiple regression analysis was physical function score.

In conclusion this study determined the risk of development of DSP in a cohort of patients who were probably already at increased risk of neurological disease due to the study entry criteria. Asymptomatic DSP was shown to be a very common finding in this group with moderately advanced HIV infection. Interestingly, however, the presence of ADSP was not a significant predictor of later development of symptomatic DSP, suggesting that ADSP and SDSP may not be part of a continuum. Importantly, in this cohort, the use of dideoxynucleoside drugs with a potential for neurotoxicity did not significantly increase the risk for DSP, in fact the trend was actually for a decrease in DSP with the use of these antiretrovirals. These data also suggest that, at least for mild neuropathy, use of ddN does not necessarily increase neuropathic symptoms.

References

High prevalence of osteonecrosis of the hip found in HIV-infection

Paul Blanchard, HIV i-Base

Osteonecrosis is, quite literally, bone death. Also known as avascular necrosis it is the loss of blood supply to the bone, which is thought to lead to bone death. Osteonecrosis most commonly affects the femoral head and may be bilateral in 50 – 80% of cases. It may be asymptomatic or present as insidious hip pain and is estimated to be responsible for 5% of all total hip replacements as a result of osteoarthritis secondary to osteonecrosis.

Osteonecrosis is a well known complication of a number of medical conditions and treatments and was first reported in HIV-infected patients in 1990. Since that date anecdotal reports have suggested an increasing frequency in the setting of HIV-infection.

A prospective study by Kirk Miller and colleagues at the US National Institutes of Health (NIH) attempted to determine the prevalence of osteonecrosis of the hip in asymptomatic HIV-infected patients and to identify risk factors associated with its development.
Magnetic resonance imaging (MRI) was used to document presence of osteonecrosis of the hip in 339 HIV-infected adults and 118 age and sex matched HIV-negative volunteers. Subjects with any current hip or groin pain were excluded. All subjects were recruited from two clinics sponsored by the NIAID and NIH Clinical Center. The patients enrolled in the study represented 63% of the total population of these clinics.

Overall 15 of the HIV-infected patients had MRI findings consistent with osteonecrosis of the femoral head. Six of these patients had bilateral hip involvement. All patients with osteonecrosis on MRI had negative radiological findings. None of the 118 HIV-negative participants had MRI evidence of osteonecrosis (p=0.015). Prevalence of osteonecrosis in this HIV-infected population was therefore determined to be 4.4%.

An analysis of possible risk factors showed an increased relative risk for osteonecrosis in patients with any lifetime use of systemic corticosteroids, lipid-lowering agents, or testosterone and in patients with a history of weightlifting or bodybuilding. Those HIV-infected patients with osteonecrosis did not differ significantly from those without in terms of age, sex, ethnicity, risk group, time since diagnosis, CD4 T-cell count, or pattern of antiretroviral use.

The researchers conclude that an extraordinary and unexpectedly high occurrence of osteonecrosis of the hip was found in this population of HIV-infected patients. They also comment that this osteonecrosis appears to be another complication of HIV disease or its related therapies that could cause considerable morbidity and require substantial resources for optimal management.


**COMMENTS**

Physical examination was performed in 168 of the patients in this study including 10 of 11 patients who were subsequently found to have osteonecrosis on MRI. Physical examination findings did not differ significantly in these patients from those with no abnormality on MRI. Physical examination is therefore unlikely to be either sensitive enough or specific enough to be a useful screening tool.

Systemic corticosteroid use is a well defined risk factor for osteonecrosis which was also identified in this study. However, only one patient had a history of prolonged exposure (2 years). In the remainder, the estimated total exposure ranged from several days to several weeks. This suggests that even short courses of corticosteroid therapy might further increase the risk of osteonecrosis in HIV-infected patients. This suggests a reevaluation of the risk/benefit analysis of these drugs in the setting of HIV-infection. Corticosteroids are currently most commonly used in this population as adjuncts in the treatment of opportunistic infections, immune reactivation syndromes and for the prevention and treatment of drug reactions.

Although serum lipid levels in this study were only marginally associated with osteonecrosis, a history of use of lipid-lowering agents, which is probably a surrogate marker for more severe hyperlipidaemia, was strongly correlated with osteonecrosis. Hyperlipidaemia is a common and well defined side-effect of the treatment of HIV-infection. It does not appear to be drug class specific and may be influenced by duration of infection, extent of viral suppression, robustness of immune reconstitution, genetics and environmental factors. In animal models a higher LDL/HDL cholesterol ratio has been identified as a risk factor for development of osteonecrosis as has a kind of intraosseous ‘obesity’ due to hyperplasia and/or hypertrophy of the fatty tissue of the femoral marrow. Although lipid-lowering agents were identified in this study as increasing the risk of osteonecrosis it is likely that they are acting as a surrogate marker for more severe hyperlipidaemia. Indeed, lovastatin actually reduced osteonecrosis risk in a corticosteroid induced osteonecrosis study.

The role of testosterone as a risk factor in this study is unclear. Both low serum testosterone level and history of testosterone use were associated with an increased risk of osteonecrosis.

It is clear from this study that plain radiographs are not useful in early detection. Hip pain and/or restriction in an HIV-infected individual should prompt a high degree of suspicion for osteonecrosis and MRI screening. The authors, however, do not recommend MRI screening for all at-risk individuals. Prophylaxis for high risk individuals (with statins for instance) should be explored and the use of systemic corticosteroids in this population reevaluated.
PATHOPHYSIOLOGY

Gene discovery offers fresh perspective on HIV/AIDS therapies

Scientists have isolated a gene that inhibits HIV-1 infection, raising hopes of a new type of natural resistance to viral activity that could be exploited in the quest for novel HIV/AIDS therapeutics.

The research, which appears on the Nature website (http://www.nature.com/nature) ahead of print publication, centres on a unique cellular gene known as CEM15, whose antiviral action is overcome by the presence of virion infectivity factor (Vif) proteins. The Vif proteins are encoded by HIV-1 and are potent regulators of viral infection and replication.

The team studied cells infected with a form of HIV that lacks Vif. They found that CEM15 interfered with the HIV lifecycle, rendering any new virus particles non-infectious.

Ann Sheehy (University of Pennsylvania) et al. write: We propose that CEM15 comprises a significant part of a form of innate antiviral resistance, and suggest that relieving its suppression by Vif may lend a fresh perspective to the area of HIV/AIDS therapies.

The search for new HIV-1 targets is becoming increasingly urgent due to the rise in resistance to standard combination drug strategies. Targeting Vif, which acts at a different stage of the viral life cycle, would circumvent the problems associated with inhibitors of reverse transcriptase and protease.

Co-author Michael Malin, from Kings College London, added: These are very significant findings and could open the door to new treatments for HIV/AIDS in the future.

If we can find a way to block the action of Vif, it would allow CEM15 to work properly and prevent HIV from spreading.

The authors caution, however, that there is still much work to be done. Ongoing work includes identifying substances that bind to and inhibit Vif in the cell, elucidating its precise mechanisms of action and structural studies of the protein.

Ref: Sheehy AM, Gaddis NC, Choi JD et al. Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein. Nature: http://www.nature.com/dynasearch/app/dynasearch.taf

Source: www.mediscover.net

Growth hormone effective in increasing thymic activity

Brian Boyle MD, for HIVandHepatitis.com

In many patients, treatment with highly active antiretroviral therapy (HAART) can lead to a significant recovery from the immunosuppression associated with advanced HIV disease. Still, some patients only experience a partial recovery, if any.

Several studies have indicated that thymic function, which may be impaired by age, HIV and other factors, is critical in determining immune recovery on HAART. In a study published in AIDS, investigators found that growth hormone, which plays a role in thymopoiesis, may increase thymic activity and CD4+ T cell counts in HIV-infected patients treated with HAART.

The prospective, open-label study, enrolled five HIV-infected men with a mean age of 52 years and CD4+ T cell count of 419 cells/mm3. All of the enrolled patients had been on stable ART for 18 months or more prior to enrollment in the study.

The patients were treated with growth hormone for six to 12 months and outcomes were compared to six closely matched patients drawn from a historical control.

The investigators found that growth hormone treatment was associated with a marked increase in thymic mass in all patients. This increase was evident by three months after growth hormone initiation and remained increased through the completion of therapy.

An analysis performed at six months of treatment showed a significant increase in thymic density and a mean increase in thymic volume of 88%. No similar changes were seen in the thymus of the control subjects. In addition to increases in thymic mass, naïve CD4+ T cells also increased significantly in all patients during growth hormone therapy. Relative to baseline levels, the mean absolute gain in naïve CD4+ cell percentage was 6% at six months, 10% at nine months, and 12% at 12 months of treatment.

The authors conclude, “At present, we believe that HIV-1-infected patients on effective ART, with radiological evidence of thymic atrophy, and with a low CD4 cell count have the greatest chance of deriving immunological benefit from [growth hormone]-mediated enhancement of thymopoiesis. In particular, individuals on effective ART who have not experienced a gain in CD4 T cells despite prolonged virological suppression may especially benefit from [growth hormone] therapy.”
“However, it is possible that such intervention may be ineffective if thymic or bone marrow reserves cannot be restored because of irreversible destruction caused by HIV-1 or advanced age.”

Ref: Napolitano LA, Lo JC, Gotway MB, Mulligan K et al. Increased thymic mass and circulating naive CD4 T cells in HIV-1-infected adults treated with growth hormone. AIDS 2002 May;16(8):1103-11


HIV long term nonprogressors have increased immune responsiveness to other viral pathogens

Brian Boyle MD, for HIVandHepatitis.com

Some HIV-infected persons are able to maintain a relatively normal immune state for extended periods, in some cases more than a decade, without taking highly active antiretroviral therapy.

In some studies, these long-term nonprogressors (LTNP) have been found to have vigorous CD8+ T cell responses to HIV, but it is not clear from these data whether this immune responsiveness is specific to HIV or is reflective of a generalized heightened immune response. In order to evaluate the specificity of heightened CD8+ T cell responses in LTNP, investigators at Case Western Reserve University examined CD8+ T cell responses to hepatitis C virus (HCV) in HCV-HIV coinfected and HCV mono-infected individuals.

The cross-sectional study, published in AIDS, involved a total of 76 patients. Forty-two of the patients were HCV monoinfected, 32 with and 10 without chronic HCV infection. Patients without chronic HCV infection had no detectable HCV RNA and had persistently normal alanine aminotransferase (ALT) over one year. Seventeen HCV-HIV coinfected patients were enrolled, 11 who were considered HCV-HIV progressors and six who were considered LTNP. These patients had both HIV and HCV antibodies and either HCV serum RNA or recombinant immunoblot assay (RIBA) reactivity. Patients considered to be HCV-HIV LTNP had no clinical manifestations of HIV infection for at least seven years and had CD4+ T cell counts >400 cells/mm3 without HIV therapy. Seven HIV monoinfected patients were enrolled, and had HIV antibody, a detectable HIV viral load, and no detectable HCV antibody. None of the enrolled patients had previously received HCV therapy. Finally, 10 healthy controls were enrolled, all of whom had no HCV or HIV antibodies.

The investigators found that five of six HCV-HIV LTNP had HCV-specific CD8+ T cell responses. In contrast, such responses were observed in only two of the 32 HCV monoinfected patients with and two of the 10 HCV monoinfected patients without chronic infection. None of the 11 HCV-HIV progressors were found to have these immune responses. In addition, the frequency of HCV-specific CD8+ T cells and number of HCV peptides recognized were significantly higher in the HCV-HIV LTNP than in other groups.

The authors conclude, “Our data indicate that HCV-specific IFN-?-producing CD8 memory cell frequency is preserved in HCV-HIV coinfected LTNP, while this is not the case for most HCV-HIV progressors and HCV singly infected individuals.

“Additionally, HCV-HIV coinfected LTNP maintained more CD8 HCV-specific IFN-?-producing cells, and targeted more HCV peptides, than did persons in other groups. These results indicate that the HIV LTNP phenotype also affects the HCV-specific CD8 memory effector pool frequency in coinfected individuals.”

Ref: Valdez H, Carlson NL, Post AB et al. HIV long-term non-progressors maintain brisk CD8 T cell responses to other viral antigens. AIDS 2002 May 24;16(8):1113-8


Red blood cells new sensitive markers for HIV disease progression?

Erythrocytes are an important extracellular reservoir of HIV-1 and quantification of this viral pool may help judge suppression of HIV-1 replication in patients with undetectable plasma viral loads, say researchers in The Lancet.

Failure of current antiretroviral therapies to completely suppress viral replication presents a major obstacle to eradication of the HIV-1 virus. This barrier remains in place, despite reduction of HIV-1 plasma RNA concentrations to levels below the limit of currently available detection systems in many patients. A number of different cell types are known to act as reservoirs or carriers for the virus, prompting calls for the design of targeted drugs.

Reports that erythrocytes bind HIV-1 immune complexes in vitro prompted Christopher Hess, of University Hospital Basel and colleagues to look for a circulating pool of virus associated with red blood cells in people with HIV-1 infection. They tested the plasma, white cells and erythrocytes from 82 chronically HIV-infected individuals using RT-PCR, and found that the HIV-1 virus
was associated with erythrocytes in 80 of these patients.

In 23 of the patients tested, erythrocyte-associated HIV-1 was detected despite the fact that plasma HIV-1 RNA had previously been undetectable by standard methods (< 20 copies/ml) for up to 32 months. Up to 82 878 HIV-1 RNA copies were detected per ml of blood in the corresponding erythrocyte samples.

Confirmation of the association between HIV-1 and this group of cells could lead to a new method for judging the suppression of HIV-1 replication in individuals with low virus levels, the authors suggest. The finding that higher numbers of HIV-1-associated erythrocytes correlated with a history of advanced clinical stages of the infection suggests that quantification of this viral pool could be used as a sensitive method for monitoring disease progression.


PAEDIATRICS

Increased risk of heart abnormalities in children born to mothers with HIV-1

A report published on The Lancet website reveals how HIV-1 infection in pregnant women is associated with persistent cardiovascular abnormalities in children shortly after birth. The authors report that, irrespective of their HIV-1 status, children born to HIV-1-infected women have substantially worse cardiac function than other infants.

The scientists, led by Steven Lipshultz of the Golisano Children's Hospital, University of Rochester, New York, used echocardiography to measure the cardiovascular function of infants born to HIV-1-infected women every 46 months, for up to five years. The group studied 93 infants infected with HIV-1 from birth, and 463 uninfected children as an internal control. Additionally, a group of 193 healthy children born to mothers who were not infected with HIV-1 was also included as an external control.

The study showed that children with HIV-1 had a higher heart rate at all ages compared with those in the internal control group, by 10 beats per minute. Furthermore, children born with HIV-1, together with those in the internal control group, had impaired cardiac structure and function up to the age of eight months, after which point there was no difference between children in the internal and external control groups. However, children born with HIV-1 had impaired heart function for the first 20 months of life, as a result of a lack of reduction in size of the left ventricle.

Co-author George Sopko stated that: Differences in the hearts structure and function in uninfected children born to HIV-infected mothers were milder and tended to dissipate over time compared to changes found in HIV-infected children.

Professor Lipshultz concluded: Impaired cardiac structure and function seem related to HIV-1-infection status in children born to women infected with HIV-1. Since LV [left ventricular] dysfunction is found in both infected and uninfected children born to women infected with HIV-1, the dysfunction could be related to the intrauterine environment. These environmental effects could result from HIV-1 and other infections, maternal and postnatal nucleoside analogue and other drug use, maternal nutrition, placental abnormalities, racial and ethnic differences, and mitochondrial dysfunction. He continued: We suggest that continuing follow-up and appropriate treatment strategies should be considered for all children born to women infected with HIV-1.

Ref: The Lancet 2002; published online June 18. Source: www.mediscover.net

OPPORTUNISTIC INFECTIONS

Paclitaxel effective for advanced AIDS-related Kaposi Sarcoma

Paclitaxel is an effective treatment for most patients with advanced AIDS-related Kaposi’s sarcoma (AIDS-KS) who have failed previous systemic chemotherapy, according to the results of a phase II study published in the 1 July issue of Cancer.

Few treatment options exist for patients with advanced AIDS-KS whose disease has progressed after receiving therapy with liposomal anthracyclines or combination chemotherapy, study author Dr. Parkash S. Gill, from the University of Southern California at Los Angeles, and colleagues note.
Dr. Gill’s team evaluated the safety and efficacy of paclitaxel in 107 male patients with advanced AIDS-KS who had failed at least one previous systemic chemotherapy regimen. The drug was given intravenously at a dose of 100 mg/m² over three hours, every two weeks.

Fifty-six percent of patients experienced a complete or partial response and the median duration of response was nearly nine months, the authors note. Almost half of the patients were taking a protease inhibitor at study entry, but the use of such agents had no bearing on the likelihood of achieving a response. Still, survival tended to be better when a protease inhibitor was used (p = 0.08).

In general, life-threatening side effects were uncommon. However, 35% of patients did experience life-threatening neutropenia and two patients died of associated sepsis, the researchers point out.

Treatment with paclitaxel was associated with a significant improvement in overall quality-of-life scores as well as improvements in KS-related symptom scores.

The present results indicate that “paclitaxel is a very active drug for this disease,” Dr. Gill told Reuters Health. “The FDA’s approval of paclitaxel for KS was actually based on data from the current study,” he added.

“Another drug that has been shown to be effective for AIDS-KS is pegylated liposomal doxorubicin (Doxil),” Dr. Gill noted. “Currently, there is a head-to-head study underway comparing paclitaxel with Doxil,” he said.

Source: Reuters Health

---

**MISCELLANEOUS**

**Study finds sexual dysfunction common in HIV-infected men receiving HAART but unrelated to protease inhibitors**

Sexual dysfunction in HIV patients has rarely been studied; sexual function has mostly been studied in this population with respect to HIV transmission.

Before the era of highly active antiretroviral therapy (HAART), it was thought that people living with HIV/AIDS had little interest in sexual relations because of the frequency of opportunistic infections and altered general health status. HAART has led to vast health improvement in people living with HIV/AIDS, enabling them to envision their life in the future.

“Clearly, the diagnosis and treatment of sexual dysfunction in these patients deserve the same attention as those in the rest of the population.

Earlier identification and treatment of sexual dysfunction should improve mood, quality of life, and therefore, adherence to treatment,” the authors wrote. They conducted a cross-sectional study of 156 ambulatory HIV-infected homosexual or bisexual men to assess and compare the prevalence and characteristics of sexual dysfunction according to the antiretroviral drug combinations they were receiving. Group A included patients who had been receiving an ongoing PI-containing HAART regimen for more than one month.

Group B included patients who had never received PI treatment. Group C included patients who had stopped taking PI therapy more than one month previously.

One hundred and fifty-six patients completed the study. The median age of the patients was 40.5  7.7 years, and the median CD4+ cell count was 415

236/mm³. Of the patients, 111 reported some degree of sexual dysfunction since the beginning of their ongoing treatment (65 of 91 group A patients; 15 of 23 group B patients, and 31 of 42 group C patients), with no significant difference among the three groups. Of 111 patients, 99 (89%) reported a reduction or loss of libido, 96 (86%) reported erectile dysfunction, 76 (68%) reported orgasmic disorders, and 65 (59%) reported ejaculatory disorders. There was no significant difference among the three groups. A history of sexual dysfunction was reported by 18% of patients before HIV seropositivity and by 32.4% of patients before the outset of antiretroviral treatment.

This study confirms the high prevalence of sexual dysfunction among HIV-infected men receiving antiretroviral therapy: 71% of patients reported some degree of sexual dysfunction. It has recently been suggested that PI treatment could be responsible for sexual dysfunction in HIV-infected men; however, the researchers found no difference in the prevalence of sexual dysfunction according to whether the HAART regimen contained PIs.

HAART regimens are known to cause adverse effects, but specific studies are required to determine whether particular antiretrovirals can cause sexual dysfunction in some patients. “This determination is important; if sexual dysfunction is indeed
caused by HAART or even if patients simply attribute sexual dysfunction to HAART, it may lead to poorer adherence to treatment, with a risk of virologic failure," the authors wrote. "Given the increased life expectancy of HIV-infected patients since the advent of HAART, their sexuality should no longer be considered only in terms of prevention of transmission. Sexual dysfunction in these patients should be specifically diagnosed and treated as in patients with other chronic diseases such as diabetes, hypertension, and depression," the researchers concluded.

Source: CDC HIV/STD/TB Prevention News Update


**ViroLogic announces launch of “viral fitness” assay for HIV infection**

ViroLogic Inc has announced the launch of the first-ever commercial laboratory test to evaluate the “replication capacity” (often referred to as “viral fitness”) of HIV.

ViroLogic’s new Replication Capacity (RC) assay measures the ability of an individual’s HIV to make copies of itself and is designed to provide useful additional information to physicians to select optimal antiretroviral therapy cocktails for their patients.

The RC test will be provided in combination with ViroLogic’s PhenoSense HIV and PhenoSense GTT drug resistance tests, “at no additional charge,” according to the company.

“Successfully treating HIV has become increasingly complex, and having more information about the patient’s individual virus may help in making better treatment decisions,” said Charles Hicks, MD, Associate Clinical Professor of Medicine, Duke University Medical Center. “As HIV drug resistance and treatment failures continue to rise, the role of the replication capacity assay in clinical decision-making may prove to be of considerable value by providing supplemental individualized patient information.”

Replication capacity is a central component of viral fitness - the ability of a patient’s virus to survive and spread in the body. When a patient is on antiretroviral therapy, HIV often mutates to become resistant to the drugs in the treatment regimen. Although these mutations decrease the efficacy of the drugs, they can also impair the virus’ replication capacity, and limit the impact of HIV in the body.

ViroLogic’s proprietary technology provides a quantitative measure of replication capacity by comparing the ability of a patient’s virus to replicate with that of a wild-type reference virus. The test result is expressed as a single percentage value. The replication capacity of wild-type virus is set at 100%, while patient results range from 0% (the virus is unable to replicate) to well over 100% (the virus can replicate more effectively than wild-type HIV).

Recent research studies suggest that replication capacity data, in combination with drug resistance information, viral load and CD4 count, may help physicians make a more informed prediction of HIV disease progression.

For example, using ViroLogic’s RC assay, physicians can identify situations in which the replication capacity of a patient’s virus is impaired because of resistance caused by exposure to antiretroviral drugs. In these cases, even though the antiretroviral drugs are no longer fully controlling replication of the virus, a physician may choose to maintain the regimen in order to keep the mutated, less “fit” strain of HIV in the patient’s body, especially if the patient has few or no other treatment options.

Source: Press Release, Virologic Inc.

---

**OTHER NEWS**

**Investigations fault HIV/AIDS cure claims**

UN Integrated Regional Information Networks

A two-year claim of an HIV/AIDS cure by 12 Nigerians has been found false in an investigation conducted by the National Institute for Pharmaceutical Research and Development (NIPRD), officials said on Wednesday.

The House of Representatives Committee on Health directed the investigations in 2000 after intense controversy was generated by the claims from both orthodox and unorthodox medical practitioners. Trials were subsequently conducted on 120 HIV/AIDS patients in nine centres across Nigeria.

“The safety of all substances presented by the claimants was ascertained in two laboratory animals - rats and mice,” Ufot
Inyang, head of NIPRD, said while submitting his report. “The relative increase in viral load level after three months of treatment with each herbal preparation was greater than 10-fold, showing that the agents had no effect on the virus,” he added.

Inyang however said some of the preparations were effective against some clinical symptoms associated with HIV/AIDS and opportunistic infections, such as diarrhoea, oral thrush and rashes. He said while some patients experienced weight gain, others lost weight. One particular preparation was effective in lowering blood pressure.

According to the report, two prominent claimants, Jeremiah Abalaka and Jacob Abdullahi, refused to submit their preparations for investigation.

Willie Ogbeide, chairman of the House Committee, who received the report, said his committee was satisfied with the result of the investigations and would act on it.

“The National Agency for Food and Drug Administration and Control, now has the power to prosecute anybody claiming to have the cure or vaccines against HIV/AIDS,” he added.

**US antitrust case could break GlaxoSmithKline’s hold on key drugs**

The largest AIDS organization in the United States has filed a federal lawsuit charging British-owned GlaxoSmithKline with anti-trust violations that could break the manufacturer’s monopolistic hold on key AIDS drugs in the United States.

AIDS Healthcare Foundation (AHF), represented by the law firm of Manatt Phelps & Phillips, challenges the pharmaceutical giant’s right to exclude competition in the markets for its anti-viral prescription drugs AZT, Ziagen and 3TC and to price these drugs well above competitive rates.

GlaxoSmithKline (GSK) controls 40% of the lucrative US AIDS drug market.

“They lied to the patent office in the 1980’s about discovering AZT’s ability to treat AIDS, and in doing so secured exclusive rights to manufacture it,” said AHF President Michael Weinstein.

“AZT was developed with federal assistance in the 1960’s, and the National Institutes of Health tested it for HIV use in the 1980’s, but Glaxo secured patents on the substance in the ’80s and locked competitors out. They then priced AZT at thirty-two times the cost of manufacture, a practice repeated with every new AIDS drug since then.”

Robert D Becker, a partner at Manatt specializing in patent law, said GSK’s predecessor Burroughs Wellcome “made matters worse by asserting the invalid patents against two generic manufacturers in the early ’90s to block cheaper generic versions of AZT. Although Burroughs successfully blocked the drugs, the validity of the patents was never decided.”

AHF, a non-profit that provides medical care to over 12,000 uninsured patients and also operates two AIDS clinics in Africa, is suing for damages created by such artificially high prices.

“It’s patent piracy that has cost untold numbers their lives and is denying treatment to millions today,” said Weinstein, “all in the name of corporate greed.”

“How many more lives could we have saved if Glaxo had not gouged the government and AHF for almost 15 years now?” asks Weinstein. “Next week, GSK will spend millions of dollars at the International AIDS Conference in Barcelona to benefit its drugs, and annually spends $500 million to market those drugs. That’s enough to provide care to one million people with AIDS in the developing world.”

AHF’s lawsuit describes a pattern of such abuse by GSK in marketing AIDS drugs. AHF charges that Glaxo’s abacavir (Ziagen) and 3TC (lamivudine) are manufactured and sold pursuant to exclusive licenses from the University of Minnesota and Emory University. Despite the fact that the drugs were developed with public assistance, GSK is doing all that it can to gouge the public and price the drugs out of reach.

AHF claims damages as a major purchaser of these medications for its uninsured patients. “Enron’s fraud cost jobs and savings,” said Weinstein. “GSK’s fraud has cost AIDS patients their lives, and has cost the federal and state governments billions of dollars in ill-gotten gain.”

AHF in the past has criticized GSK for spending too little on assisting people with AIDS in the developing world, which by Glaxo’s own account is about $55 million over the last decade.

“That’s three-tenths of one-percent of Glaxo’s AIDS drug sales,” said Weinstein.

In calling for pricing based on cost, Weinstein contrasts the annual price of triple-combination anti-retroviral care charged by GSK, generics manufacturer Cipla, and the Thai government: “Glaxo charges the U.S. government $10,600 annually, Cipla’s price is $440, and the Thai’s charge $336. Since Glaxo didn’t invent or discover AZT, Ziagen or 3TC, what could possibly justify
the difference? In developing nations, Glaxo’s so-called preferential prices are also up to double that charged by Bristol Myers Squibb, Merck and Pfizer,” said Weinstein.

The suit is being filed in United States Federal Court for Central District of California (Western Division). Manatt attorneys John F. Libby, Robert D. Becker, and Noel S. Cohen represent AHF in this action.

SOURCE AIDS Healthcare Foundation

---

**ON THE WEB**

**FURTHER REPORTS FROM ICA 2002**

**Adherence Research Roundup From the International AIDS Conference**

Coverage provided by Myles Helfand

Hundreds of medical researchers at the XIV International AIDS Conference testified to something most reasonable people already know: the more a healthcare professional helps HIV-positive people who miss their doses of antiretroviral medications, the more likely these people are to stop missing doses.

Full text at:


**Highlights of Presentations on Gender From Barcelona**

Coverage provided by Barbara Jungwirth

Women are the fastest-growing group of people with HIV/AIDS, yet the majority of clinical studies on any HIV treatment have been done on men. Slowly researchers seem to be getting the message from activists that attention must be paid. Gender can be an important issue when it comes to adherence and responses to treatment. Compared to previous International Conferences on AIDS, Barcelona had more, but still not enough, presentations that dealt with issues of gender and HIV. Many of these, however, were more concerned with the psychological and social factors influencing women’s access to — and use of — HIV services. Among those were several studies on adherence to medication schedules and clinic visits.

Full text at:


**Additional ICA2002 reports at thebody.com**

Visit The Body’s AIDS 2002 page for detailed coverage on research presented in Barcelona, audio and video highlights of major events and speeches, and links to other reputable sources of information on the International AIDS Conference.

Full text at:


**Medscape Conference Coverage, based on selected sessions at the XIV International AIDS Conference**

Available now — next-day reports of the highlights of the Barcelona meeting, summarized and analyzed by our expert faculty.

Topics covered include:

* New data on optimal first-line therapy
* PI therapy and heart disease
* Limited benefits of treatment interruptions
* New report confirms HIV superinfection
* Treatment of primary HIV infection
* Update on investigational antiretrovirals

Coming soon: additional post-meeting reviews, certified for CME.

Available at:

Monkey Puzzles

Jon Cohen

As a growing number of vaccines move through the pipeline toward clinical trials, experiments with monkeys are producing puzzling data — and doubts.

The first full-scale trial of an AIDS vaccine is scheduled to end in November, and the world will soon learn whether it works. A second product will move into a large efficacy trial this fall. Earlier in the pipeline, the array of AIDS vaccines entering human studies is more diverse than ever before. “The pipeline is dramatically improved in many ways from five to six years ago,” says Peggy Johnston, who heads the AIDS vaccine program at the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland. But, Johnston cautions, “significant scientific and operational challenges remain.”


Full text at: http://aidsscience.org/Science/2325.html

Diversity Considerations in HIV-1 Vaccine Selection

Brian Gaschen, Jesse Taylor, Karina Yusim, Brian Foley, Feng Gao, Dorothy Lang, Vladimir Novitsky, Barton Haynes, Beatrice H Hahn, Tanmoy Bhattacharya, Bette Korber

Globally, human immunodeficiency virus-type 1 (HIV-1) is extraordinarily variable, and this diversity poses a major obstacle to AIDS vaccine development. Currently, candidate vaccines are derived from isolates, with the hope that they will be sufficiently cross-reactive to protect against circulating viruses. This may be overly optimistic, however, given that HIV-1 envelope proteins can differ in more than 30% of their amino acids. To contend with the diversity, country-specific vaccines are being considered, but evolutionary relationships may be more useful than regional considerations. Consensus or ancestor sequences could be used in vaccine design to minimize the genetic differences between vaccine strains and contemporary isolates, effectively reducing the extent of diversity by half.


Full Text at: http://aidsscience.org/Science/2354.html

Confronting the Limits of Success

Jon Cohen

Six years ago, new cocktails of anti-HIV drugs transformed prospects for infected people in industrialized countries. Now, serious limitations have become apparent.

To veteran AIDS researchers, “Berlin” is shorthand for “gloom and doom, 1993.” “Vancouver” translates to “elation, 1996.” “Durban” means “waking up to the global crisis, 2000.” The tags refer to the field’s Zeitgeist in the years these cities hosted the international AIDS conference. For this year’s conference in Barcelona, Spain, the tag line could well be “the limits of success.”


Full text at: http://aidsscience.org/Science/2320.html
Mycobacterium Avium Complex and Atypical Mycobacterial Infections in the Setting of HIV Infection

Mark A. Jacobson, MD, University of California San Francisco, Judith A Aberg, MD, Washington University, Saint Louis

*Mycobacterium avium* complex (MAC) consists of several related species of mycobacterium that are ubiquitous in the environment. MAC rarely causes disease in individuals with a normal immune system. In patients with AIDS, however, it is one of the most common serious opportunistic infections. Among HIV-infected individuals, disseminated MAC has historically occurred almost exclusively in patients with a CD4 count <50 cells/cu mm. Colonization of the respiratory or gastrointestinal (GI) tract by MAC can occur without evident morbidity; however, MAC colonization of these sites indicates that patients are at increased risk for developing disseminated MAC infection. Highly active antiretroviral therapy (HAART) has been associated with reductions in AIDS-related mortality, days of hospitalization, and the incidence of new OIs. However, there have been numerous reports of aberrant clinical presentations of MAC since the introduction of HAART.

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-05-01-05

Management of Anal and Cervical Dysplasia in Men and Women, Presentation

Joel M. Palefsky, MD at the Medical Management of AIDS


http://hivinsite.ucsf.edu/InSite.jsp?page=cfmma-08

Anaemia, neutropenia, and thrombocytopenia: pathogenesis and evolving treatment options in HIV infected patients

Fully updated: Alexandra Levine, MD presents a comprehensive review of the management of anaemia, neutropenia, and thrombocytopenia in HIV-infected patients.

Medscape HIV/AIDS CME Spotlight 2002


Quick reference guide to antiretrovirals

A new edition of Malte Schutz’s popular overview of antiretroviral dosing, side-effects, interactions, and resistance, incorporating the latest data from recent meetings.

Medscape HIV/AIDS 2002

http://www.medscape.com/updates/quickguide

Identifying and managing morphologic complications of HIV and HAART

Morphologic complications continue to be observed in patients receiving HAART. Body habitus changes include fat accumulation, lipoatrophy, and HIV-associated wasting. Anthropometry, dual-energy x-ray absorptiometry, and imaging methods (CT, MRI) are most useful for detecting fat redistribution syndromes, while bioelectric impedance analysis is useful for determining and monitoring wasting. Various clinical interventions, including diet and exercise, switching antiretroviral agents, the use of lipid-lowering and insulin-sensitizing agents, recombinant human growth hormone therapy, and plastic surgery, are under investigation for the treatment of morphologic changes. Prospective, controlled clinical trials are needed to determine the long-term efficacy of these approaches.

AIDS Read 12(3) 2002


Achieving adherence with antiretroviral medications for paediatric HIV disease

AIDS Reader 12(4) 2002

Factors influencing antiretroviral adherence for 42 HIV-positive children were elicited from primary caregivers, and the perspectives of families and clinicians regarding success with adherence were compared. Interviews in preferred language
(Spanish or English), chart reviews, and visual analogue scales (VAS) were used. Adherence was high by traditional markers of prescriptions filled (100%), doses reported taken (97%), and appointments kept (88%). Clinicians estimated slightly but not significantly lower adherence than did families using the VAS. Sixty-four percent of families reported barriers to adherence, and 30% reported strategies that differ from those in the general adherence literature. Adherence strategies devised by families depended heavily on family support and resolution of disclosure issues in the household.


“Natural” resistance to HIV: Is the evidence good enough to design an effective vaccine?

Paul Palumbo, Joan Skurnick, Christine Rohowsky-Kochan, and Donald Louria

What is the evidence for a protective immune response to HIV that supports the quest for a prophylactic vaccine? During the early years of the epidemic, there was little acceptance of the notion of natural resistance and scant evidence that the kind of resistance that would prevent infection could be generated. More attention should have been focused on the early studies of sexual partners of haemophiliacs, most of whom remained uninfected despite repeated exposure. The research community focused (quite appropriately) on virus strain, genital viral load, infectivity per contact, and ability of the virus to propagate in mucosal cells, but we should have suspected then that some of the noninfectivity related to host resistance. We will refer to this as “natural immunity or resistance” primarily to distinguish it from immunity induced by a vaccine.

Source: AIDScience Vol. 2, No. 11, June 2002

Full text at:
http://aidscience.org/Articles/AIDScience022.asp

Efficacy and safety of once-daily antiretroviral therapy

Brian A. Boyle, MD

Efforts at antiretroviral simplification are not only likely to improve virologic response and HAART durability but also likely to have the serendipitous effect of significantly improving quality of life. Again, this sounds like a statement of the obvious, but it becomes most apparent when one considers once-daily therapy: If patients could take their medications once a day, at whatever time they settle on as being most convenient, and then not have to think about medications or HIV again, they would not be “tied down” by medications and it would “be easier”.

As noted in a recent editorial on once-a-day therapy, “patients are already pushing the once-a-day agenda in the belief that less frequent dosing will mean the treatment has less impact on quality of life, and that their lives will not so much be run by the demands of their medication.”

Full text at:

Therapeutic implications of acute hepatitis C infection

Elmar Jaeckel, MD

The hepatitis C virus’s greatest weapon might very well be its silence. It is an infection that is initially asymptomatic and often goes unrecognised, anywhere from several years to more than two decades after the infection has established itself in the liver. Because of this, countless individuals in this country and elsewhere are not aware that they are, in fact, chronically infected with the virus.

Full text at:
http://www.prn.org/prn_nb_cntnt/vol7/num2/jaeckel_frm.htm

Liver Disease in HIV: An Update

Vincent Soriano, MD, PhD

In the United States, it is estimated that 30% of the 800,000 people living with HIV are coinfected with the hepatitis C virus (HCV). Similar rates have been documented in Western Europe, although the actual number of HIV-infected individuals in
some countries is not well defined.

The magnitude and potential ramifications of HIV/HCV-coinfection is even more alarming in Spain, where Dr Vincent Soriano suggested that at least half of the 130,000 HIV-positive people in the country are coinfected with HCV. In turn, Spain has become a hotbed for coinfection research and has yielded studies that have helped to address some of the most important questions regarding follow up and treatment facing clinicians today.

Full text at:
http://www.prn.org/prn_nb_cntnt/vol7/num2/soriano_frm.htm

New antiretrovirals in development: The View in 2002
Roy Trip Gulick, MD, MPH

Despite the fact that 16 antiretrovirals are approved for use in the United States, there is an indisputable need for new anti-HIV compounds that have potent and durable efficacy profiles, unique resistance patterns, patient-friendly dosing schedules, and minimal toxicities. To provide PRN with a glimpse of drugs currently snaking their way through the development pipeline, Dr Roy Trip Gulick returned to the podium at the February 2002 PRN meeting to discuss his observations of data presented over the past few years. A summary of his presentation along with data presented at the Ninth Conference on Retroviruses and Opportunistic Infections (CROI), held in February in Seattle is provided here.

Full text at:
http://www.prn.org/prn_nb_cntnt/vol7/num2/gulick_frm.htm

Update on IL-2: where it’s been and where it’s going
Richard T Davey Jr, MD, FACP

Perhaps no other drug in the history of HIV/AIDS treatment research has been more extensively studied than recombinant interleukin-2 (IL-2). It has been evaluated in numerous proof-of-concept and phase II clinical trials both alone and in combination with antiretrovirals or with other immune-based therapies involving a broad spectrum of patients, including those in the acute, chronic, and late stages of HIV disease. Ironically, however, it still lacks a licensed therapeutic indication in HIV. This may change sometime during the next few years. Massive phase III clinical trials are now under way to address fundamental questions regarding the clinical utility of IL-2 treatment. These results along with other data from pivotal IL-2 clinical trials will be reviewed by the US Food and Drug Administration and may help carve out a niche for the drug in the standard-of-care for HIV-positive people.

Full text at:
http://www.prn.org/prn_nb_cntnt/vol7/num2/davey_frm.htm

Insights into HIV-specific CD4+ T cell immunity
Ronald B Moss

Greater understanding of the role of HIV-specific immunity remains fundamental to current and future therapies to prevent and treat HIV infection. The induction of HIV-specific immunity in seronegative individuals might involve similar or different effector cells of the immune system compared to individuals who are infected and maintain a reservoir of latently infected cells on or off antiviral drugs. This short review will focus on recent understanding of HIV-specific immunity in HIV-infected individuals. Specifically, the role of the CD4+ T helper cell in HIV-specific immunity will be addressed.

Source: AIDScience Vol. 2, No. 12, June 2002

Full text at:
http://aidscience.org/Articles/AIDScience023.asp

Updated knowledgebase chapters:
Cytomegalovirus
William L Drew MD, PhD and Jacob Lalezari MD, updated 6/02.

Cytomegalovirus (CMV) has been a major cause of morbidity and mortality in patients with AIDS. Epidemiologic studies
indicated that through 1992 nearly half of HIV-infected patients eventually developed CMV end-organ disease including chorioretinitis, esophagitis, colitis, pneumonia, and central nervous system disease. With the advent of highly active antiretroviral treatment (HAART) there has been a dramatic decline in the occurrence of CMV disease in AIDS patients to approximately 5-10% of previous estimates. A diagnosis of CMV disease can be based on clinical evaluation (eg, CMV retinitis) but often requires tissue biopsy with histologic evidence of viral inclusions and inflammation (eg, CMV colitis). A positive CMV culture of blood, urine, or even biopsy tissue may only reflect active infection rather than true end-organ disease. Detection of CMV antigens or nucleic acids in tissue specimens are alternative, but less conclusive, methods for making a diagnosis of CMV disease.

Full text at:
http://hivinsite.ucsf.edu/InSite.jsp?page=kb-05-03-03

The Switching Spiral: a triumph of hope over benefit?

from The AIDS Reader
Graeme Moyle MD, MBBS

The HIV therapy market is expanding. Patients are not only living longer and therefore continuing therapy but also taking more antiretroviral medications simultaneously. Persons already receiving therapy represent the vast majority of the treatment market; patients who are currently naive represent a minority at most clinics. So, while there remains interest in competing over which drugs to begin with, there is also considerable interest by pharmaceutical companies in generating sales and gaining market share by encouraging physicians to switch their patients from their current regimens, which have often served them well for a number of years, to the new or alternative agents. The usual justification, often based on short-term or even in vitro data, is that the new or alternative drug carries a lower risk of causing or contributing to a future adverse event.

Full text at:

Peripheral Neuropathy

Liz Highleyman

Of the many symptoms associated with HIV/AIDS and its treatment, peripheral neuropathy (PN) can be among the most painful and debilitating. The most common estimate is that about one-third of people with AIDS experience some degree of nerve damage. However, PN usually occurs in the later stages of HIV disease, and many people experience mild or no symptoms.

Nerve damage may be caused by HIV itself, by opportunistic infections (OIs) such as cytomegalovirus (CMV), or as a side effect of certain anti-HIV drugs, notably ddl (Videx), ddC (Hivid), and d4T (Zerit). In people with HIV/AIDS, PN most often affects the feet, the lower legs, and later the hands, causing numbness, tingling, and/or pain. Fortunately, there are medical treatments and other measures people with HIV/AIDS can take to ameliorate neuropathy symptoms and improve their quality of life.

Full text at:

The push for once-daily HAART: a call for caution

from Medscape HIV/AIDS eJournal[TM]
Andrew D Luber, PharmD

Advances in the management of HIV have resulted in significant declines in both mortality and AIDS-related opportunistic infections. As a result, the management of HIV-infected individuals has shifted from morbidity/mortality prevention to a chronic disease management model for many patients. With this change in treatment strategy, interventions to improve patient adherence and quality of life have become more prominent. Several recent articles on the Medscape HIV/AIDS Web site have reflected the growing focus of drug developers on once-daily antiretroviral agents and regimens, with varying degrees of success. While the use of entirely once-daily antiretroviral regimens has been highly anticipated by both providers and patients, it should be appreciated that there are many potential pitfalls among all three classes of antiretroviral agents when constructing such regimens.

Full text at:
Enhancing Adherence to Antiretrovirals: Strategies and Regimens

Valerie E. Stone, MD, MPH, from Medscape HIV/AIDS eJournal[TM]

There is widespread acknowledgement that successful treatment with highly active antiretroviral therapy (HAART) requires the patient to maintain consistent adherence to the prescribed regimen on a long-term basis. This article aims to provide an update on key issues in adherence to HAART, based on results from published articles and abstract presentations during the past one to two years.

As HIV-treating clinicians endeavor to optimize and enhance their patients' adherence to HAART, it is necessary to have a strategy regarding: (1) assessing the patient's readiness to start and adhere to HAART; (2) choosing a regimen to which the patient is likely to adhere; (3) choosing and using interventions to improve HAART adherence; and (4) monitoring adherence to HAART on an ongoing basis. This article will review the available evidence regarding each of these 4 topics and their implication for clinical practice.

Full text at:

High Doses of Riboflavin and Thiamine May Help in Secondary Prevention of Hyperlactatemia

Grace A. McComsey, MD; Michael M. Lederman, MD, from The AIDS Reader ®

Lactic acidosis and its less severe form, symptomatic hyperlactatemia, are increasingly recognized complications of nucleoside reverse transcriptase inhibitor (NRTI) therapy for HIV infection.[1,2] While acute management of these complications involves discontinuation of NRTIs, the safety of resuming therapy with these agents is not well established. Because continuation of suppressive antiretroviral therapy with an NRTI-sparing regimen is not always feasible, strategies that may permit safe resumption of NRTI therapy in this setting are needed.

Thiamine (vitamin B1) and riboflavin (vitamin B2) are both important for intact mitochondrial function. Thiamine is a coenzyme of pyruvate dehydrogenase, and thiamine deficiency can lead to defective pyruvate metabolism and accumulation of lactate.[3,4] Riboflavin is converted to flavin mononucleotide and dinucleotide, both serving as necessary cofactors for the electron transport chain. Recent reports suggest dramatic improvement of lactic acidosis after administration of these vitamins.[5-7]

We report our experience with two HIV-infected patients for whom the addition of vitamins B1 and B2 allowed resumption of NRTI-containing antiretroviral regimens without recurrence of hyperlactatemia.

Full text at:

Conference Report

HAART and Prevention of HIV Transmission, June 6-7, 2002; Atlanta, Georgia

from Medscape HIV/AIDS, Myron S Cohen, MD

HIV is the dominant infectious disease of the 20th and (most likely) 21st centuries. Accordingly, effective interventions not only to treat HIV, but also to prevent its acquisition, are of great importance. Tremendous resources have been spent on understanding the routes of transmission of HIV, identifying the populations affected, and defining and testing prevention strategies.

There is a range of possible HIV prevention strategies, of which the most thoroughly evaluated are the promotion of behaviour change, the use of barrier methods such as condoms (and potentially the diaphragm), and the control of sexually transmitted diseases (STDs), which act as cofactors for HIV transmission. Other approaches currently being studied include: Topical microbicides; Vaccines; Male circumcision; and Use of antiretroviral therapy.

Of these, the potential role of antiretroviral therapy is particularly important; indeed, it could be argued that every dose of antiretroviral therapy that is administered has public health implications. Although the effects of antiretroviral therapy on HIV transmission currently remain unclear, transmission by patients receiving therapy definitely occurs, whether it is studied or not. Furthermore, the use of antiretroviral therapy for prevention is an evolving subject, and the pharmaceutical industry is continuing to develop new drugs, some of which might be specifically targeted to prevention of transmission.

Full text at:
PUBLICATIONS AND SERVICES FROM i-BASE

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

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

Copies have been distributed with this issue of HTB and more can be ordered free in bulk. There are also French and Chinese translations of this booklet. To order copies, see below.

The latest issue of Positive Treatment News (PTN)
The latest issue of Positive Treatment News, our magazine for positive people, looks at adherence (missed any pills recently, need any advice?), the latest information about side effects and treatments, and the benefits and risks of joining a drug trial or study. There is also a detailed look at weight loss and what can be done about it, the official treatment guidelines, salvage therapy and treatment information provision for the African community. To order copies, see below.

Changing treatment: an updated guide to second-line and salvage therapy
This is a 16-page non-technical guide to resistance testing, intensifying treatment, treatment interruptions, switching drugs to avoid side-effects, experimental drugs and drugs available through expanded access programmes.

HIV i-Base treatment guides are reviewed every six months to keep them up-to-date.

Since the previous edition several new treatments have become available to use in salvage therapy:

• The nucleotide tenofovir (Viread) has been approved for use in second-line therapy. This drug can work against virus that has low-level resistance to AZT, 3TC and other nucleosides.
• T-20 has started trials in the UK for people resistant to current drugs - with a limited expanded access programme expected to follow later in the year. T-20 will have activity against any resistant virus.

Other changes to this edition are to the sections on phenotypic resistance testing, treatment interruptions and Mega-HAART (and the Optima Study) and changing treatment because of side effects.

The sections on expanded access and experimental treatments have also been updated. To order copies, see below.

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

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

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

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

Order i-Base publications via the internet, post or fax
People with internet access can use our site to order publications. You can access our publications online or subscribe to receive our publications by email or by post; and you can order single copies or bulk deliveries by using the forms at:

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

Copies of publications can also be ordered by post or fax using the form on the back page of this journal. These methods of ordering are suitable for all our publications: HIV Treatment Bulletin (HTB), Positive Treatment News (PTN) and all our treatment guides and new reports.

All publications are available free of charge — including bulk orders for the UK or single copies for other countries.
Subscription Fax-Back Form

Please use this form to amend subscription details for HIV Treatment Bulletin (DrFax) and/or Positive Treatment News, and to order single or bulk copies of other publications.

Name: __________________________________   Position: __________________________
Organisation: _____________________________________________________________________
Address: _____________________________________________________________________
_____________________________________________________________________
Tel: ____________________________________ Fax _____________________________
E-mail: _____________________________________________________________________

HIV Treatment Bulletin (HTB) □ by Email (PDF format) □ by Post

Guide To Avoiding and Managing Side Effects (August 2001)
IN ENGLISH
1 □ 5 □ 10 □ 25 □ 50 □ 100 □ Other______
Also available in FRENCH _______ and CHINESE _______

Introduction to Combination Therapy (December 2001)
IN ENGLISH
1 □ 5 □ 10 □ 25 □ 50 □ 100 □ Other______
Also available in several other languages - please state how many of each of the translations you require
FRENCH _______ ITALIAN _______ SPANISH _______ GREEK _______

1 □ 5 □ 10 □ 25 □ 50 □ 100 □ Other______

Positive Treatment News (PTN) from Spring 2002
1 □ 5 □ 10 □ 25 □ 50 □ 100 □ Other______

Paediatric HIV Care - March 2001 - Report from i-Base Paediatric Meeting
1 □ 5 □ 10 □ Other______

Adherence planners and side effect diary sheets - In pads of 50 sheets - for adherence support
1 □ 5 □ 10 □ Other______

Please fax this form back or email a request to HIV i-Base:
020 7407 8489 (fax) subscriptions@i-Base.org.uk