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TREATMENT ACCESS

From Talk to Action in Fighting AIDS in the Developing Countries: *8th Retrovirus Conference Opening Session*

Laurence Peiperl, MD, HIV InSite Medical Editor

In the final address of the opening session, economist Jeffrey Sachs addressed the "utter, complete, one hundred percent failure of international policy to address this crisis in the poorer countries of the world." The essence of the crisis in Africa, he maintained, results not from "exceptionalism," but from poverty, noting that AIDS has occurred against a background of health problems for which solutions exist, but which have not been addressed because of insufficient resources. The international response to AIDS in Africa, he asserts, has been "a few tens of millions of dollars and a lot of hand-wringing, but no real assistance," since the total annual contribution of about $70 million amounts to $3 per HIV-infected individual per year in Sub-Saharan Africa.

Noting that World Bank programs have addressed issues ranging from grief support to replacement of lost workers, but not treatment, Sachs criticized donor agencies for failing to acknowledge the responsibility of rich countries to make treatments available in poor countries. While he finds activism targeted at large pharmaceutical manufacturers to be often appropriate, he noted that drug companies have agreed to provide substantial discounts to developing countries. In his view, these agreements are undermined by lack of rich country support, because many affected African countries cannot afford to pay even the minimum production costs of effective antiretroviral regimens.

Sachs outlined a plan to provide treatment for several million Africans with AIDS over the next few years, at a cost to rich countries of about $2 billion per year. Comparing this figure to the $8 trillion dollars in capital gains the US has experienced in the past decade, and noting that tax cuts of trillions of dollars are being considered in the US, he characterized $2 billion as "rounding error" to the macroeconomist — the equivalent of a levy of $2 per person per year in rich countries.

The first element of Sach's plan, therefore, is support by rich countries, with acknowledgement by the United States that, if treatment interventions can be shown to be effective, then rich countries should be prepared to fund them. Second, pharmaceutical companies would, with US government commitment to the program, provide antiretroviral drugs at their manufacturing cost. In return, the rich country markets for the drugs would be preserved, "and we should be strong supporters of that."

Thirdly, the scientific and research establishment would test propositions that antiretroviral therapy could in fact be applied effectively in poor countries, and determine what kind of protocols can work. For example, this operational research might address adherence, and whether CD4 count and viral load monitoring are in fact necessary for effective treatment. In this scenario, the World Bank would fund scientific proposals to test such medical and epidemiologic hypotheses.

In closing, Sachs emphasized that, "We now know that at least we can try to do something…. What we need to do urgently is, finally, to move."

Source: HIV InSite
http://hivinsite.ucsf.edu/

Ref: Sachs JD. Keynote Lecture: From Talk to Action in Fighting AIDS in Developing Countries. 8th Conference on Retroviruses and Opportunistic Infections; February 4-8, 2001; Chicago, Illinois. Abstract L3.

Webcast of complete lecture available online at:
http://www.retroconference.org/2001/hearlec.cfm

UNAIDS calls for new deal between pharmaceutical companies and society

With poor access to HIV treatments common in developing countries, Dr Peter Piot, Executive Director of the Joint United Nations Programme on HIV/AIDS (UNAIDS), has called for greater efforts in improving access, including greater cooperation between the pharmaceutical industry and the rest of society.

"The combined need for continuing innovation and the moral demands for global access to life-prolonging HIV medicines calls for nothing less than a new deal between the pharmaceutical industry and society," said Dr Piot in a UNAIDS statement. The agency suggests that multiple innovative strategies are needed, including tiered pricing, competition between suppliers to reduce prices, regional procurement, licensing agreements, use or reinforcement of health safeguards in trade agreements, and new funding mechanisms.

"Improving access to care and treatment is a complex challenge, requiring the involvement of all sectors, including governments, nongovernmental organizations, and both the research and development-based and generics pharmaceutical industries," Dr Piot pointed out. "Improving access to the more technologically complex elements of care, such as treatment of opportunistic infections and antiretrovirals, acts as an entry point for improving access to broader elements of care and vice versa," Dr Piot noted. "More drugs will catalyse better health care delivery systems. Better health care delivery systems will promote greater capacity to deliver affordable medical technology."

Source: Reuters Health

US trade action threatens Brazilian AIDS programme

Gavin Yamey, BMJ

International health agencies have condemned the US government for threatening the Brazilian policy of providing free drugs to patients infected with HIV. The US government has initiated legal proceedings against Brazil, through the

World Trade Organisation's dispute settlement body, claiming that Brazil's production of generic HIV drugs breaks international laws on patent protection. Brazilian laws provide patent protection to foreign drug companies if they manufacture their product in Brazil. These laws have allowed local Brazilian companies to manufacture generic HIV drugs at low cost. The United States has complained to the World Trade Organisation that this requirement for local production discriminates against the US pharmaceutical industry.

Bernard Pécoul, director of the Médecins Sans Frontiàres' Access to Essential Medicines campaign, said: "The lives of hundreds of thousands of patients depend on this system [in Brazil]. The US action will also intimidate countries which would like to take up Brazil's offer to help them produce AIDS medicines."

Brazil's health ministry estimates that the number of deaths from AIDS has halved since it started distributing free HIV drugs. A ministry spokesperson said, "This policy has resulted in a significant improvement in the quality of life of people living with HIV and AIDS, as well savings to the Brazilian government amounting to $422m (£281m)." Concern is growing among aid agencies that the trade rules administered by the World Trade Organisation are hindering access to essential medicines in the developing world. Although the rules allow poor countries to produce their own generic drugs, these countries' attempts to do so have often been met by US threats of trade sanctions (BMJ 2000;320:207) or legal challenges by pharmaceutical companies.

In a case that goes to court on 5 March, a coalition of 40 drug companies is suing the South African government with Nelson Mandela named as a defendant for manufacturing generic HIV drugs. "Limiting generic manufacturing capacity is in the interests of the pharmaceutical industry," said Ellen `t Hoen of Médecins Sans Frontiàres. "And the US, by its trade threats, is sending out the message, `don't mess with our pharmaceutical companies.' "

Oxfam launched its own campaign (Cut the Cost) this week, which calls for a change in the World Trade Organisation's trade rules to make it easier for poor countries to manufacture low cost drugs. Justin Forsyth, Oxfam's director of policy, said, "The World Trade Organisation must change the rules that the drug industry is now using to cripple cheap, local competition, which in turn is inflating the cost of new and patented medicines."

In a move that could start an international price war on HIV drugs, an Indian generic drugs manufacturer, Cipla, has announced that it will sell triple combination HIV therapy to Médecins sans Frontiàres for $350 a year per patient. The cost to governments will be $600 a year per patient. Five major drug companies promised last year to cut the costs of its HIV drugs in the developing world (BMJ 2000;320:1357), but their prices are still three times those offered by Cipla.

Oxfam's Cut the Cost campaign is at

www.oxfam.org.uk/cutthecost

Source: BMJ 2001;322:383 (17 February)

Brazil May Flout Trade Laws to Keep AIDS Drugs Free for Patients

Brazil's AIDS drug program—which produces HIV-fighting medicines locally at a drastically reduced cost and offers them free to HIV-positive Brazilians, most of whom would not be able to afford the drugs at their regular prices—is coming under fire from multinational drug companies that are demanding international patent laws be respected. The two most important drugs in the program are Merck's efavirenz and Roche Holding's nelfinavir [*Ed. – Merck and Roche are in fact distributors of these drugs and not the patent holders in Brazil*], which together comprised about 36 percent of Brazil's AIDS program spending in 2000 of $319 million, spurring the government to threaten local generic production if prices are not reduced by the manufacturers. However, the problem is more than just the two drugs, because Brazil will need to increase its importation of AIDS drugs by five times before 2005, spending as much as $1.7 billion to treat HIV-positive patients.

A statute in Brazilian law permits the move to generics after three years of patent protection if a drug is considered vital. While the clause is being contested by the U.S. government and drug companies to the World Trade Organization, there is no denying that the program has cut the number of AIDS-related deaths in Brazil by 50 percent over the past four years and slowed HIV transmission to well below World Health Organization predictions.

Ref: Wall Street Journal (12/02/01) P. B1.
www.wsj.com

Source: CDC HIV/STD/TB Prevention News Update

Roche Open to Discuss Patent Rights of AIDS Drug With Brazil

Roche Holding announced on Friday that it would be willing to confer with Brazil and with international trade organizations about the patent rights for its AIDS drug nelfinavir, following a threat from the nation that it would begin allowing generic firms to produce the drug if prices were not reduced. A Roche spokesman said that the firm believes there is a need to explore, with the help of trade experts, the international patent rights and under what circumstances a country may overrule those rights. The United States has brought Brazil's anti-AIDS program and its threat to the World Trade Organization, which will determine whether Brazil must amend its legislation.

Ref: Agence France Presse
www.afp.com

Source: CDC HIV/STD/TB Prevention News Update

Crusading Indian firm takes on might of Glaxo SmithKline: Cipla offers anti-HIV drugs at a fraction of rivals' prices

Indira Gandhi decided 30 years ago that her country would go it alone, undercut the international drug giants, refuse to honour their patents and make its own cut-price versions of

their medicines. Now India's leading drug company, Cipla, is at the centre of the battle for cheap medicines elsewhere in the developing world, and it is taking on the British giant Glaxo SmithKline.

Cipla is offering a three-drug anti-HIV cocktail of stavudine, lamivudine and nevirapine for just $600 (£430) to governments and $350 to Médecins sans Frontières, the volunteer doctors who have set up AIDS clinics in sub-Saharan Africa. The drug cocktails sell for between $10,000 and $15,000 in the west.

The offer puts pressure on the five big producers of AIDS drugs, including Glaxo SmithKline, that have offered to discount their prices by up to 85% for African states.

Glaxo SmithKline has warned Cipla off from selling its cheap copy of Combivir - a combination of AZT and 3TC (lamivudine) - in Ghana and Uganda, saying it has patent rights in those countries. But Cipla's offer, particularly to MSF, risks wrong-footing the drug giants.

Sir Richard Sykes, chairman of Glaxo SmithKline, says the generic companies are "pirates". He claims the price of medicines is not the only reason why millions of people with HIV/AIDS are dying. The political will to spend money on medicines is sometimes lacking, and developing countries do not have the clinics and doctors that are vital to ensure that AIDS drugs are properly used, he says.

India exports vast quantities of cheap generic drugs to the Middle East, Latin America and Africa. Yet Cipla faces new patent legislation enforced under trade deals which threaten its export business. Dr Yusuf Hamied, Cipla's chairman, says the bargain price he has now placed on the table is a response to the massive disaster that AIDS represents. Unlike last month's Indian earthquake, AIDS is an "entirely predictable tragedy", he says. "In this disaster there is room for everybody."

Cipla can afford to undercut its western rivals because, in common with India's 23,000 drug firms, it spends almost nothing on research and development. As soon as a new drug hits the market, Indian scientists break down its molecular structure, helped in their task by the internet, where pharmaceutical formulas are freely available.

Dr Hamied says without cheap generic drugs, millions of poor would have no access to medicines. "We have never been against patents. We have been against monopoly, because monopoly leads to higher prices," he says.

Source: Guardian Unlimited.

http://www.guardian.co.uk/Archive/Article/0,4273,4135941,00.html

GSK to review drug pricing policy: Pharmaceuticals giant reacts to criticism over costs to poor countries

GlaxoSmithKline, under pressure to make its drugs more widely available in poor countries, is reviewing its approach to pricing and patent enforcement. At a meeting with institutional investors, GSK promised to present a new policy framework outlining its stance on affordable medicines by the end of June. Jean-Pierre Garnier, chief executive of the newly merged Anglo-American company, has said he will make the issue a priority. However, he has stressed that drug companies cannot achieve anything alone and that the problems go deeper than the price of drugs. Several investors, concerned that a bad public image could damage GSK's long-term share price, attended Wednesday's meeting in central London. They included Friends Ivory & Sime, Hendersons, Morley Fund Management, Jupiter and the Universities Superannuation Scheme.

"Investors want the company to have something that looks more like a coherent strategy towards access to medicines," said one investor. "They have to raise their game in understanding how seriously the public takes this issue and how seriously investors take it." GSK was targeted by Oxfam this week as part of a campaign to highlight the allegedly damaging implications of tighter global patent regulations on public health in poor countries. GSK was criticised, in particular, for appearing to defend patents on Aids drugs in Ghana and Uganda and for backing legal action against the South African government, which is seeking the right to import cheaper medicines. "GSK has some very interesting (access) programmes, but they don't seem to have a thoroughly thought-out approach to this problem," said one investor. "The real crunch is over intellectual property and whether the company can be flexible without damaging other parts of its business."

Drug companies say poverty is a greater barrier to health than the price of patented medicines. They are also concerned that, if cheap copies of drugs become widely available in poor countries, they could undermine their markets in the west. Oxfam insists high drug prices can have a huge impact on people with limited access to health care. "We still disagree about the impact of patents on the price of drugs," said Sophia Tikell, senior policy adviser at Oxfam. "Any review of policy will not be serious unless it addresses this issue."

Source: Financial Times; Feb 16, 2001.

www.ft.com/healthcare

Oxfam launches stinging attack on drug industry over cheap medicines ban

British charity Oxfam has accused the global pharmaceutical industry and the world's rich nations of waging "an undeclared drugs war" against poor countries by refusing to allow them to produce low-cost equivalents of some life-saving medicines.

In a stinging attack on the world's pharmaceutical giants at the launch of its "Cut the Cost" campaign, Oxfam said developing countries should be allowed to produce copies of drugs to treat HIV/AIDS, respiratory infections and diarrhoea in children. The charity said the price of such medicines was prohibitively high for many because of exclusive marketing rights created by patents held by major drug companies. And expensive medicines are "one of the major causes of poverty and suffering" with some 11 million people worldwide dying each year from preventable disease, it said. "Locally-produced, low cost medicines are a lifeline for poor people," said Oxfam. "India, for instance, can make antibiotics at an eighth of the price of patented versions." But they cannot do so because of the patents.

The charity singled out GlaxoSmithKline, warning it would throughout 2001 be targeting the British juggernaut that was born in December from fusion between GlaxoWellcome and SmithKline Beecham. Oxfam said it wanted GlaxoSmithKline to state clearly how it intends to fulfil its commitment "to maximise affordable medicines in the developing world" and to issue reports on the progress it is making in this regard. The pharmaceutical group must also "set a fair price for their medicines, based upon the ability of people in poor countries to pay for them." Oxfam also called on the group, which has an annual turnover of more than one billion dollars, to dedicate a percentage of it sales towards research into diseases rampant in the Third World.

Responding, a spokesman for GlaxoSmithKline said the company "much regrets" Oxfam's statement, and that it "offers little or no acknowledgement of the company's long-standing commitment and contribution to meeting the challenge to increase the access to medicine in the developing world." He in particular quoted SmithKline's programme to eliminate lymphatic filariasis, a tropical disease, and of GlaxoWellcome's actions programme against malaria and tuberculosis. "But we will study their recommendations carefully," the spokesman said.

Oxfam said that under World Trade Organisation (WTO) rules, patents on medicines produced by the drug industry are protected for 20 years. "This is the shadowy side of globalisation. The WTO must change the rules that the drug industry is now using to cripple cheap, local competition, which in turn is inflating the cost of new and patented medicines," it added.

Source: Agence France-Presse
http://ww2.aegis.org/news/afp/2001/AF010241.html

Companies Weigh Offer of Royalties for AIDS Drugs Aimed at Africa

Two U.S. drug companies appear to be weighing an Indian generic drug maker's offer to pay them 5% royalties in exchange for permission to sell knockoff versions of their patented anti-AIDS drugs in developing countries.

Bristol-Myers Squibb Co. and Pfizer Ltd. have both promised to respond soon to the offer from Bombay-based Cipla Ltd., according to letters made available by Cipla. The Indian drug company produces its own version of anti-retroviral drugs used to fight AIDS, and recently jolted pharmaceutical companies by offering to sell an AIDS "cocktail" to an international aid organization at a much lower price than the multinational pharmaceutical companies had offered poor countries.

Cipla says it hasn't received responses from two other companies - GlaxoSmithKline PLC of the U.K. and Boehringer Ingelheim Ltd. of Germany - to its proposal, made in a Dec.19 letter that requested a "timely response." Glaxo told The Wall Street Journal ft was considering Cipla's offer but had reservations about ft.

The idea of a 5% royalty is unlikely, by itself, to resolve the current quandary over how to protect patent rights while making drugs available to poor countries hit hard by the AIDS pandemic. Glaxo, after all, has already rebuffed Cipla's bid to sell AIDS drugs in Ghana, where Glaxo claims patent protection. Still, it is risky for drug companies to brush off Cipla's royalty offer, because doing so could hand Cipla a weapon to enter those markets anyway, through a manoeuvre called "compulsory licensing."

Under compulsory licensing, a government can force patent holders to grant licenses to generic drug makers. Unless there is a "national emergency," though, the generic company first has to establish that ft tried to get a license on "reasonable commercial terms" but was rebuffed.

Patent holders "don't want to issue licenses," says James Love, a Washington-based activist who has been involved in talks between Cipla and international aid groups that are hoping to distribute AIDS drugs free of charge. Mr. Love, of the Ralph Nader group Consumer Project on Technology, says that with compulsory licensing, it is "up to the governments" to decide who gets a license. He says citizens groups are starting to put pressure on African governments to try to get low-priced AIDS drugs even if it means going generic.

Pfizer expects to respond to Cipla's proposal later this month, a spokesman said yesterday. "We think it unlikely that an agreement could be reached with Cipla," the spokesman, Bob Huber, said. But Pfizer will ask for additional information about Cipla, including its roster of board members and manufacturing processes. Pfizer advocates donation programs as the best way to expand patient access to vital medicines in Africa and elsewhere. "It makes little difference if a medication is priced at $5,000 a year or $500 a year in many developing nations," Mr. Huber said. "Both are beyond the reach of most patients."

Bristol-Myers didn't respond to a request for comment on Cipla's offer. A spokesman for Boehringer Ingelheim said that he was unaware of Cipla's letter but that "any kind of offer would have to be discussed."

Glaxo spokesman Phil Thomson said, "The best thing we can say is we have received [Cipla's offer] and it's under consideration." But he cautioned that ',we need to look at the royalties" and said he couldn't say when the company would respond to Cipla's offer. Right now, Glaxo said, it is focused on selling the two products Cipla referred to in its letter, lamivudine and zidovudine, through a United Nations program in which drug companies negotiate with developing countries to sell their AIDS drugs at a discount.

From Cipla's point of view, a compulsory license would be an easier way to get its AIDS drugs into sub-Saharan Africa than selling to aid groups. Cipla is expected to meet in coming days with the group Doctors Without Borders to try to iron out an agreement to sell the group an AIDS cocktail at a price of $350 per patient per year. But even if a deal is reached, Doctors Without Borders could face problems distributing the drugs in countries with strong patent protections. Cipla's strategy is to "somehow persuade the governments to recognize compulsory licensing," says Jesal Shah, a research associate with SG Asia Securities, based in Bombay. He adds, "Cipla has been trying to break into the sub-Saharan region with its AIDS drugs for quite some time now.

Cipla officials say winning a compulsory license wasn't

necessarily the intent of the December letter to the AIDS-drug patent holders. "We don't have a definite plan of action" if the drug companies turn down the offer, says Amar Lulla, Cipla's joint managing director, who signed the letters. "I don't think we would be able to afford litigation or to pressure governments."

The World Trade Organization, by 2005, will require members to have laws in place to protect pharmaceuticals from copycat manufacturers such as Cipla. But countries can include compulsory licensing in their laws. The licenses would require an adequate payment to the patent holder, though determining what's adequate could be sticky. Cipla is offering up to 5% of sales1 depending on how strong a patent claim the other company has in a particular country. Cipla says it drew the figure from a year-old submission by a U.S. pharmaceutical trade group that cited 5% as the average pharmaceutical royalty rate. But a spokesman for the group, Pharmaceutical Research and Manufacturers of America, says the 5% is a "low-end, conservative estimate."

Although some developed countries such as Canada have used compulsory licensing in the past to keep drug costs low, poor countries haven't been jumping on the idea. Even in India, some pharmaceutical companies have mixed feelings about a strong compulsory-license measure being considered in their country. After all, it could come back to haunt them if they develop their own drugs. Government officials worry that foreign aid could dry up if they push for compulsory licenses, says Anand Grover, a Bombay public-interest lawyer specializing in AIDS issues.

U.N. officials are cheering the idea of royalties, but from the sidelines. Jonathan Quick, director of the World Health Organization's department of essential drugs, notes that royalties are a "business arrangement," and that U.N. officials decided this week that "it's not our role to get in the middle of commercial patent discussions."

Source: The Wall Street Journal

OTHER NEWS

Drugs need not be stopped because of neutropenia in HIV-infected patients

Neutropenia in the presence of HIV infection is rarely severe and is not usually associated with additional infection, according to data from a prospective study carried out in London. Patients participating in the study continued drug therapy during the episodes of neutropenia, which resolved on mean average within 21 days.

Dr David A. J. Moore and colleagues at Chelsea and Westminster Hospital followed all adult HIV-infected patients at their clinic who developed absolute neutrophil counts of less than 1000 cells/mL. They report their findings in the February 1st issue of Clinical Infectious Diseases. From 17 000 inpatient and outpatient visits, 87 patients with new neutropenic episodes were identified. All but 3 patients were being treated with potentially myelosuppressive therapy, most with zidovudine, lamivudine and/or co-trimoxazole. For those with a first episode, the mean CD4+ cell count was 153/mL. The mean CD4+ cell count was lower, 103/mL, for subsequent episodes of neutropenia. First episodes averaged 25 days in duration, compared with 17 days for subsequent episodes. Only 3 patients presented with neutrophil counts less than 200 cells/mL. Only 4 serious and 8 more moderate infections developed during an episode of neutropenia. Two of the serious infections occurred in subjects with neutrophil count nadirs less than 200 cells/mL. Patients with infections had a lower mean CD4+ cell count than those without infections, 64/mL vs 126/mL.

"An observational strategy may be the optimal management in the absence of sepsis," Dr Moore's team concludes.

Ref: Clin Infect Dis. 2001;32:469-476.
Source: Reuters Health

Effective antiretroviral therapy resolves HIV organ-specific complications in 3 children

Highly active antiretroviral therapy (HAART) is known to reduce the incidence of opportunistic infections in HIV-infected patients, and a recent study of 3 HIV-infected children finds that it also resolves the organ-specific complications of the virus itself.

In a study reported in the February 1st issue of Clinical Infectious Diseases, Dr Frank T. Saulsbury from the University of Virginia Health System in Charlottesville describes the clinical course of 3 HIV-infected children who were treated with HAART.

The first case involved a perinatally infected boy who was diagnosed with a dilated cardiomyopathy at age 7 months. After several admissions for pulmonary oedema, the patient was given zidovudine, lamivudine, and ritonavir at age 3.5 years. The patient's CD4 cell count and viral load level steadily improved, and 1 year later he was asymptomatic with normal cardiac function.

The second patient, a perinatally infected girl, was diagnosed with red cell aplasia at age 12 months. She was treated for a likely parvovirus B19 infection until the work-up results proved negative. The patient remained anaemic and reticulocytopenic for 18 months before being treated with zidovudine, lamivudine, and ritonavir at age 2.5 years. Her CD4 cell count and viral load level improved steadily, and her haemoglobin concentration normalized.

The final patient, also a perinatally infected girl, was diagnosed with a nephropathy at age 21 months. At age 3.5 years, ritonavir was added to the zidovudine and didanosine regimen that she was receiving. Within 2 months, her CD4 cell count and viral load level had improved. By 12 months, the proteinuria had resolved, and urinary protein excretion was normal.

"To date, the major benefit of HAART has been a decline in morbidity and mortality due to opportunistic infections," Dr

Saulsbury points out. "Although there is very little information concerning the value of HAART for patients with organ-specific complications, the present report suggests that a variety of noninfectious complications of HIV infection are amenable to HAART."

Ref: Clin Infect Dis. 2001;32:464-468.
Source: Reuters Health

Seroconversion in Kenyan sex-workers linked with reduced HIV-specific immune response

HIV-specific CD8+ T cells play an important role in controlling viraemia, the authors explain, but maintenance of such a circulating cytotoxic T lymphocyte (CTL) presence may require ongoing antigenic stimulus. Dr Rupert Kaul, and colleagues, from the University of Nairobi in Kenya, examined 11 late seroconverters, who had previously met criteria for HIV-1 resistance, for evidence of HIV-1–specific CD8+ responses. Dr Kaul's findings follow the preliminary description of 6 highly exposed, previously uninfected sex workers who had seroconverted after they stopped continual exposure to HIV-1. Pre-seroconversion data were available for 6 of the 11 women. Four of the 6 women had HIV-1–specific CTL responses ranging from 5 months to 18 months before seroconversion, the authors report.

Seroconversion was not associated with contraceptive method or occurrence of sexually transmitted diseases over the preceding year, the researchers note, but overall reduction in sex work—taking a break or reducing the number of daily clients—was significantly associated with late seroconversion. Only 2 of the 11 late seroconverters had not experienced a decrease in sex work. While there was no decrease in the number of daily clients, 1 of the 2 women reported increased condom use in the year preceding seroconversion, followed by decreased condom use at the time of seroconversion.

In 6 of 7 women who took at least a 2-month break from sex work, HIV-1–specific responses were no longer seen in peripheral blood mononuclear cells, the report indicates, and 3 of 4 women who retired from sex work experienced a loss of such responses. Three such women who returned to sex work redeveloped HIV-1–specific responses after a lag of 12.4 months on average, according to the results.

"The association of HIV-1 seroconversion with reduced sex work seems initially counterintuitive, but it might be compatible with a loss or diminution of HIV-1–specific CTL in the absence of ongoing antigenic stimulation," the authors conclude.

Ref: J Clin Invest. 2001;107:273-275,341-349.
Source: Reuters Health

Prevalence and correlates of anaemia in a large cohort of HIV-infected women

Researchers studied a cross section of HIV infected women, to compare the prevalence and correlation of anaemia occurring in patients with asymptomatic HIV infection versus clinical HIV. Test subjects included racially mixed 2056 HIV-positive and 569 HIV-negative women who were categorized demographically and clinically, as their immunological and virological relationships to anaemia were studied. In overall comparison between all test subjects regardless of race, the data concluded that anaemia was more prevalent among HIV-positive patients at 37 percent compared to 17 percent of HIV negative women.

Among the HIV positive women, 44.9 percent of black women showed a stronger incidence of anaemia with haemoglobin levels of < 12 g/dl, followed by 25.7 percent of whites and 24.8 percent of Hispanics. Using mean corpuscular volume (MCV) as another standard for testing revealed that women with low MCV were more susceptible to anaemia regardless of HIV status.

Ref: Levine AM, Berhane K, Masri-Lavine L et al. Journal of Acquired Immune Deficiency Syndromes (01/01/01) Vol. 26, No. 1, P. 28.
www.jaids.com

Source: CDC HIV/STD/TB Prevention News Update

HIV-related fatigue relieved by psychostimulants

Fatigue, a common manifestation of HIV disease that strongly affects quality of life, is effectively treated with methylphenidate or pemoline, according to a report published in the February 12th issue of the Archives of Internal Medicine.

Dr William Breitbart, and colleagues, from Memorial Sloan-Kettering Cancer Center in New York, assessed the safety and efficacy of psychostimulants in the treatment of HIV-related fatigue by studying the outcomes of 109 HIV-infected, fatigued patients randomised to receive 60 mg of methylphenidate, 150 mg of pemoline, or 8 capsules of placebo daily. While 41% and 36% of subjects receiving methylphenidate and pemoline, respectively, experienced significant improvement in their fatigue, only 15% of placebo-receiving subjects achieved this benefit. The improvement with psychostimulant use was significant on several self-reported rating scales. In addition, the rate of improvement in Piper Fatigue Scale total scores was significantly greater when psychostimulants were given. The researchers found that both psychostimulants were equally effective in treating fatigue. Improvement in fatigue was also significantly associated with improvement in measures of depression, psychological distress, and overall quality of life, they note. Hyperactivity and jitteriness were significantly more common among psychostimulant users, but severe side effects were relatively uncommon.

"This study reflects the first empirical demonstration of the effectiveness of psychostimulants for the treatment of HIV-related fatigue," the authors state. "The use of psychostimulants in the clinical management of fatigue in patients with HIV disease is most appropriate as part of a comprehensive approach," the investigators point out. "This approach would include the identification and treatment of AIDS-related conditions that can cause fatigue, such as anaemia, as well as the judicious use of combination antiretroviral therapies to reduce viral load and restore immune function."

Ref: Arch Intern Med. 2001;161:411-420.
Source: Reuters Health

Studies underway on metabolic side effects of antiretrovirals

The Committee for the Evaluation of the Metabolic Complications of HAART recently met to review the status of four research studies it is sponsoring to explore side effects of antiviral medications:

- A study to develop a case definition of lipodystrophy;
- A prospective observational study of several patient cohorts from 11 countries in Europe, the US and Australia totalling over 20,000 participants to look for increases in rates of heart attacks, strokes, and diabetes;
- A meta-analysis of recently initiated metabolic studies of major clinical trials networks and other related studies; and
- A retrospective review of medical records in the HIV database of the US Veterans Administration system to determine whether there was a significant increase in the rate of heart attacks and strokes following the introduction of HAART.

These efforts are characterized by collaboration, starting with the Committee itself. The Committee was created in response to a request by the European Medical Evaluation Agency (EMEA) for more information regarding the possibility that antiviral medications might cause an increase in rates of heart attacks or strokes. It consists of representatives from eight pharmaceutical manufacturers of HIV antiviral medications, plus members from academia, the European Union (EMEA-CPMP Pharmacovigilance WP), the US Food and Drug Administration, and the community. Committee co-chairs are David Pizzuti, MD, Vice President of Medical Affairs at Abbott Laboratories and Professor Ian Weller, head of the Department of STDs, Royal-Free and University College Medical School, London.

In another example of collaboration, the prospective observational study will combine data from a large number of existing HIV research cohorts, some of which normally compete for research resources and subjects. Finally, the principal investigators of large metabolic studies from several networks are collaborating to harmonize the data collected in each study as much as possible, laying the groundwork for future meta-analysis.

The pharmaceutical companies comprising the Committee are Abbott Laboratories, Agouron Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, DuPont Pharmaceuticals, GlaxoSmithKline, Hoffmann-La Roche and Merck. Collectively, these firms are committing approximately five million dollars to support the four research studies.

Each research study is conducted by an academic researcher as principal investigator and has its own steering committee. Research proposals were subjected to peer review before they were approved and funded by the Committee. The Committee receives regular status reports and critically evaluates progress on the individual studies.

These important research studies are expected to significantly advance our understanding of the side effects associated with HIV antiviral medications but are not intended to provide definitive answers.

Lipodystrophy Case Definition Study

Principal investigator: Andrew Carr, St. Vincent's Hospital, Sydney

Design: Case-control study

Objective: Formulate a sensitive, specific, simple, cost-effective and universally applicable tool for diagnosis of lipodystrophy syndrome(s).

Sites: 35 clinical sites in Europe, Asia, Australia, and North and South America

Expected Recruitment: 800 subjects

Projected Completion: 3rd quarter of 2001

This is the first major systematic effort in this area. Four hundred patients with lipodystrophy will be identified along with 400 control patients. The study has a goal of recruiting at least 160 women. A "training dataset" will consist of 250 cases and 250 controls. The study will identify the variables that differentiate the cases from the controls. These variables will be used to develop one or more definitions of lipodystrophy. The definition(s) will then be tested against the "validation dataset" consisting of the remaining 150 cases and 150 controls. This will be the first careful definition of lipodystrophy, and may not apply to special populations such as infants and children or to certain ethnic groups.

Data Collection on Adverse Events of Anti-HIV Drugs (The DAD Study)

Principal investigator: Jens D. Lundgren, MD, Copenhagen HIV Program

Design: Prospective cohort study

Objective: Attempt to determine whether there is an increased risk for cardiovascular events when patients are receiving HAART

Sites:11 cohorts in Europe, the US and Australia

Expected Recruitment: Over 20,000 subjects

Projected Completion: 3rd quarter of 2002

Subjects will be followed for an average of two years, generating at least 30,000 patient-years of data. Rates of cardiovascular disease events will be compared in time intervals since initiation of antiviral therapy to study whether rates increase with longer exposure to therapy, and further to compare these rates with large studies of the general population. The DAD study is powered to determine whether HAART therapy results in at least a doubling of risk. It will not likely have sufficient power to determine how much each antiviral drug might contribute to cardiovascular risk.

Meta-analysis of metabolic studies

Principal investigator: Janet Darbyshire, PhD, Medical Research Council Clinical Trials Unit, London

Objective: Attempt to discern whether information gathered previously in already completed trials or in ongoing prospective trials can derive information on the incidence of metabolic

abnormalities with specific types of HAART therapy

Projected Completion: 2003

This effort is based on the data collected in existing research trials. The more similar the data sets, the more powerful the results of the meta-analysis. A feasibility study will be conducted and include review of some completed and ongoing studies and may produce a first meta-analysis. As part of this effort, the principal investigators of the major metabolic studies in naïve patients (ACTG384, CPCRA FIRST, INITIO, and ATLANTIC), have collaborated to align the metabolic data they are collecting. This will maximize the power of the meta-analysis and will result in a model dataset for studies of metabolic complications. The major metabolic studies will follow subjects for several years, which will increase the value of the data they produce. The meta-analysis will be conducted following the completion and unblinding of the data sets.

Retrospective review of Veterans Administration database

Principal investigators: Barbara R. Phillips, PhD, and Samuel A. Bozzette, MD, PhD, Veterans Affairs (VA) San Diego Healthcare System, University of California, San Diego, California.

Design: Retrospective analysis

Objective: Assess the impact of highly active antiretroviral therapy (HAART) and classes of antiretroviral drugs on serious, adverse cardiovascular and cerebrovascular events in the context of a changing force of mortality

Data Characteristics: Over 20,000 patient-years

Projected Completion: 3rd quarter of 2001

This study has been designed to determine whether there has been a large increase in the rate of heart attacks and strokes among people using HAART. The dataset has certain limitations, including a lack of information about whether patients were smokers or not (a major risk factor for cardiovascular disease) and limited information on other cardiovascular risk factors. Due to the small number of women in the VA system, data will be analysed for men only. This analysis is intended to provide a rapid evaluation of how much HAART therapy increases the risk of these serious events.

Lactic acidosis in pregnant women receiving d4T (stavudine) and ddI (didanosine): EMEA issue statement

The US FDA issued a statement on January 5th 2001 cautioning on the use of d4T and ddI during pregnancy. This statement and an accompanying letter to healthcare providers from Bristol Myers Squibb was reproduced in full in HTB Vol 2, No 1.

The statement is also available at:

www.fda.gov/medwatch

On January 26th the European Agency for the Evaluation of Medicinal Products (EMEA) also issued a statement concerning this issue and concluded that "…at present there is insufficient information to decide whether pregnancy is an additional risk for lactic acidosis."

The full text of the EMEA statement is reproduced below.

London 26th January 2001 EMEA/CPMP/228/01

PUBLIC STATEMENT

Reports of lactic acidosis in pregnant women treated with Zerit® and Videx®

The EMEA's scientific committee, the CPMP, has been made aware of seven cases of lactic acidosis in pregnant women treated during pregnancy with the combination of Zerit® (stavudine) and Videx® (didanosine). Three of these cases were fatal. Stavudine and didanosine are nucleoside reverse transcriptase inhibitors (NRTIs) indicated for use in combination with other antiretroviral agents for the treatment of HIV- 1 infection.

Of the three women who died, one also had pathologically confirmed hepatic steatosis and two had pancreatitis. Two of these maternal deaths occurred in a multinational, randomised clinical study. One patient was taking the triple combination therapy of didanosine/stavudine/nelfinavir whilst the other was treated with the triple combination didanosine/stavudine plus an investigational protease inhibitor. The third death and the four additional non-fatal cases of lactic acidosis were identified through worldwide post-marketing surveillance. Of the three women who died, one baby survived; the other two died prior to the mother's death, at between 32-36 weeks gestation.

Lactic acidosis, sometimes fatal, is a known side effect of NRTIs. Consequently the Summaries of Product Characteristics of all NRTIs used in the treatment of HIV infection (stavudine, lamivudine, abacavir, zidovudine, didanosine and zalcitabine') warn of the risk of lactic acidosis, which may be fatal. Prescribers are also informed of the need for caution when prescribing to any patient (particularly obese women) with a history of hepatomegaly, hepatitis or other known risk factors for liver disease.

Lactic acidosis is usually associated with severe hepatic damage and other organs may also be affected. Lactic acidosis can occur a few weeks to several years after the beginning of treatment with NRTIs. Symptoms which may be indicative

of the development of lactic acidosis include: digestive symptoms (nausea, vomiting, anorexia, abdominal pain, diarrhoea), respiratory symptoms (dyspnea), neuromuscular symptoms (cramp, myalgia, paraesthesia) or a non specific general deterioration (asthenia, weight loss).

The CPMP has carefully reviewed the available data and considers that at present there is insufficient information to decide whether pregnancy is an additional risk for lactic acidosis. It is also uncertain whether any increased risk of lactic acidosis is specific to stavudine and didanosine or whether it might be increased with all combinations of nucleoside analogues. The EMEA also wishes to draw attention to the fact that, except for the use of zidovudine in the prevention of materno-foetal transmission of HIV, the use of nucleoside analogues during pregnancy is not recommended unless the potential clinical benefit clearly outweighs the potential risks.

The CPMP and National Agencies have requested additional information from all concerned marketing authorisation holders and these issues will be evaluated further by the CPMP for the whole class of NRTIs.

These NRTIs are marketed under the following tradenames (in brackets): lamivudine (Epivir®); abacavir (Ziagen®); zidovudine (Retrovir®); zalcitabine (Hivid®); the combination product lamivudine/zidovudine (Combivir®) ; and the combination product lamivudine/zidovudine/abacavir (Trizivir®)

EMEA, 7 Westferry Circus, Canary Wharf, London, E14 4HB, UK.

Tel: +44 (0)20 7418 8400

http://www.eudra.org/emea.html

UK to Start Trials of New Cervical Cancer Vaccine

Britain's Cancer Research Campaign (CRC) has announced plans to initiate human trials of a new vaccine against cervical cancer. The vaccine is intended to boost the body's immune system against human papillomavirus (HPV), which is associated with 95 percent of cervical cancer cases. In the initial trial, 24 women will receive different doses of the vaccine to see how their immune systems respond. Results of study will be available in mid-2002, and, if successful, the CRC and the Imperial Cancer Research Fund will launch a larger trial to see if the optimum dose helps prevent HPV infection.

Source: CDC HIV/STD/TB Prevention News Update

Anal HPV Infection Common in HIV-Positive and High-Risk HIV-Negative Women

A new report in the Journal of Infectious Diseases (2001;183:383-391) indicates that anal human papillomavirus (HPV) appears to be common in HIV-positive and HIV-negative women who are at high-risk for infection. Researchers from the University of California at San Francisco studied 251 HIV-positive women and 68 women who had similar risk factors but were not infected with HIV. Approximately three-quarters of the women with HIV and two-fifths of the HIV-negative women had anal HPV DNA. The researchers also discovered that in a subset of 200 women for whom cervical HPV information was also available, anal HPV was much more common.

Source: CDC HIV/STD/TB Prevention News Update

Plasma Cysteine Deficiency and Decreased Reduction of Nitrososulfamethoxazole with HIV Infection.

The aim of these studies was to determine whether HIV-infected patients have a plasma thiol deficiency and whether this is associated with decreased detoxification of the toxic metabolites of sulfamethoxazole. Reduced, oxidized, protein-bound, and total thiol levels were measured in 33 HIV-positive patients and 33 control subjects by an HPLC method utilizing the fluorescent probe bromobimane.

The reduction of sulfamethoxazole hydroxylamine and nitrososulfamethoxazole by plasma and the plasma redox balance in the presence of nitrososulphamethoxazole were also determined by HPLC. Reduced plasma cysteine was significantly ($p < 0.0001$) lower in HIV-positive patients (13.0 +/- 3.0 ?M) when compared with control subjects (16.9 +/- 3.0 ?M). Although there was no difference in oxidized, protein-bound, and total cysteine, the thiol/disulfide ratios were lower in HIV-positive patients.

Reduced homocysteine was elevated in patients. Plasma from HIV-positive patients was less able to detoxify nitrososulfamethoxazole than control plasma. These findings show that the disturbance in redox balance in HIV-positive patients may alter metabolic detoxification capacity, and thereby predispose to sulfamethoxazole hypersensitivity.

Ref: Naisbitt DJ, Vilar FJ, Stalford AC et al. AIDS Res Hum Retroviruses 2000 Dec;16(18):1929-1938.

Capravirine clinical trials restricted: Additional safety evaluation required

Pfizer announced that it has restricted use of its investigational drug capravirine for some patients in clinical trials based on results of a 12-month animal toxicology study, which demonstrated an unexpected finding of vasculitis. This decision was reached in discussions with the U.S. FDA.

Vasculitis, an inflammation of the blood vessels, was observed in animals that received very high doses of capravirine in the 12-month toxicology study; this finding was not seen in previously conducted animal safety studies. Pfizer is working closely with the FDA to conduct additional animal toxicology studies to further evaluate the safety profile of capravirine. To date, no cases of vasculitis have been detected in patients receiving capravirine in the Pfizer trials.

Capravirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is presently the subject of phase II and III clinical trials to determine the drug's safety and efficacy in people living with HIV. 650 patients are currently enrolled in six separate studies. The FDA is permitting treatment-experienced patients, who previously have failed NNRTIs but are responding well to capravirine, to continue their current capravirine drug regimens. The remaining patients will discontinue use of capravirine but will remain on study protocols.

"Patient safety is always paramount in our clinical studies," said Dr. Barry Quart, Senior Vice President, Pfizer Global Research & Development and Site Director, La Jolla Laboratories. "We remain committed to the capravirine program and expect to resume clinical trials once these safety issues have been resolved."

Capravirine is being developed by the La Jolla Laboratories of Pfizer Global Research and Development and will be marketed by Agouron Pharmaceuticals, a Pfizer company.

Source: Company press release

COMMENT

Data on the efficacy of capravirine in NNRTI experienced patients was detailed in a poster presentation at the 8th CROI [Abstract 323]. Wolfe and colleagues revealed that less than 30% of subjects had achieved a plasma viral load <50 copies/mL when given a new regimen containing capravirine, nelfinavir and 2 NRTI's. These are disappointing results considering patients were PI-naïve and that both NRTI's used were new to the patients. It is difficult to interpret this data as providing any evidence that capravirine retained activity in this NNRTI-experienced group.

Gilead announces start of early access program for investigational anti-HIV agent tenofovir DF in United States and France

Programs to Begin in Germany, Italy, Spain and the United Kingdom upon Regulatory Clearance

Gilead Sciences, Inc. have announced the initiation of a limited expanded access program to provide tenofovir disoproxil fumarate (tenofovir DF) to people with advanced human immunodeficiency virus (HIV) infection in the United States and multiple countries in the European Union. Regulatory review has been concluded and programs are open for registration in the United States and France. Early access programs will be initiated in Germany, Italy, Spain and the United Kingdom as regulatory approvals are obtained. Tenofovir DF is an investigational reverse transcriptase inhibitor, dosed as a single tablet once daily, currently being evaluated in combination with other agents in multinational Phase III clinical studies as a potential treatment for HIV infection. Expanded access programs are part of an effort by the U.S. Food and Drug Administration (FDA), European regulatory agencies and the pharmaceutical industry to make investigational drugs available during the later stages of clinical development for the treatment of serious or life-threatening diseases. "Patients with advanced HIV disease can rapidly run out of viable treatment options and often rely upon access to experimental therapies, said James Rooney, MD, Vice President of Clinical Research and leader of the worldwide Tenofovir DF Early Access Program at Gilead. "Initiating this limited program is our first step toward providing patients in greatest medical need with access to tenofovir DF.

The U.S. program will make tenofovir DF available to patients at least 18 years of age with HIV infection who have had a CD4 count less than or equal to 100 cells/mm 3 and an HIV RNA level of greater than or equal to 10,000 copies/mL by PCR within the past two months. Patients must also have failed treatment with at least two protease inhibitors (PIs) or one PI and one non-nucleoside analogue reverse transcriptase inhibitor. Additionally, patients with a CD4 cell count between 100 cells/mm 3 and 200 cells/mm 3 and an AIDS- defining opportunistic infection within the last 90 days may also be eligible. The U.S. program was designed with input from HIV patient advocates and representatives of HIV/AIDS community organizations. The viral load and CD4 cell count entry criteria for the U.S. program were established to insure that patients with the most advanced disease and in greatest need of a new antiretroviral therapy would have priority access during the initial stages of the program.

The French program will make tenofovir DF available to patients through an Authorisation Temporaire d'Utilisation de Cohorte. Design of early access programs in the European Union varies from country to country, according to specific regulatory guidelines. Patients will receive tenofovir DF 300 mg dosed as a single tablet once daily. Gilead will advise physicians to include, in addition to tenofovir DF, at least one new antiretroviral agent that has not been previously administered to their patients.

Gilead intends to submit the NDA to the U.S. FDA and the Marketing Authorisation Application to the European Medicines Evaluation Agency for tenofovir DF in mid-year 2001.

COMMENT

For more information regarding the tenofovir DF early access program or to request registration materials, physicians in the United States may call 1-800-GILEAD-5 and those within Europe may call +33-1-44-90-34-46.

Mortality from liver disease increasing in HIV-positive patients

End-stage liver disease has become a major cause of death among patients infected with HIV, according to a report in the February 1st issue of Clinical Infectious Diseases. Many HIV-seropositive patients are coinfected with hepatitis C virus (HCV), the authors explain, and the course of HCV-related liver disease from chronic active hepatitis to end-stage liver disease and death is accelerated in these patients.

Dr Barbara McGovern, and colleagues, from New England Medical Center, Boston, Mass, examined the causes of death among HIV-positive patients who died at their institution, Lemuel Shattuck Hospital in Jamaica Plain, Mass, during 1991 (group 1), 1996 (group 2), and 1998 to 1999 (group 3). Most of the patients likely acquired HCV and/or HIV infection as a result of injection drug use, the report indicates. Along with antiretroviral therapy, most of the individuals received other potentially hepatotoxic agents, the researchers note, and most patients who underwent testing had antibodies to HCV and to hepatitis B virus (HBV).

Only 11.5% of the deaths in group 1, during the years before highly active antiretroviral therapy (HAART), resulted from complications of end-stage liver disease, Dr McGovern and associates found. When HAART was being introduced, during the time of the group 2 patients, the mortality from end-stage liver disease rose only slightly, to 13.9% of the deaths. In group 3, however, well into the era of HAART, 50% the deaths were associated with end-stage liver disease, the authors report, with the remainder distributed among sepsis, cytomegalovirus disease, cryptococcal meningitis, and other causes.

"End-stage liver disease has become the leading cause of death of HIV-seropositive patients at our institution," the authors conclude. "This trend is occurring in the background of a dramatic decline in the incidence of opportunistic infections and the rate of AIDS-related mortality in the era of HAART."

"HIV providers need to evaluate HIV and HCV simultaneously," Dr McGovern suggested. "Just as they get a CD4 cell count and HIV RNA on that first visit, they need to check hepatitis serologies and HCV RNA, and vaccinate as needed and get a liver biopsy in patients who are viraemic."

Ref: Clin Infect Dis. 2001;32:492-497.
Source: Reuters Health

C O M M E N T

In the majority of abstracts assessing mortality in HIV-infection in the era of HAART presented at the 8th CROI, liver disease was the 2nd largest cause of death after AIDS events.

TREATMENT GUIDELINES

First European guidelines for HIV-1 drug resistance testing

The first European guidelines on HIV-1 drug resistance testing have been published in the February edition of the authoritative peer review journal AIDS (Vol 15 No 3, February 2001).

The guidelines, produced by the EuroGuidelines Group (EGG), were developed to help clinicians decide when and how to employ new diagnostic tests that indicate levels of HIV drug susceptibility in those being treated for HIV disease. In particular, the guidelines will help clinicians decide which combinations of drugs are most appropriate when initiating treatment, for those who have failed one or more previous drug regimens, and for optimal antiretroviral therapy in children and during pregnancy.

Launching the guidelines, Veronica Miller, a member of the EGG from the Centre for Internal Medicine at J W Goethe University in Frankfurt, said: "HIV-1 drug resistance testing could have a major role to play in patient care in the future. At present, however, there are no common guidelines throughout Europe and no consistency in terms of technology, reporting or reimbursement of resistance testing. These guidelines seek to address this situation for the first time."

In addition to guidance on the interpretation of HIV resistance tests, the guidelines also provide recommendations on procedures for sample collection, how to select a laboratory at which test samples are to be analysed and the level of reporting clinicians should expect from their chosen laboratories.

While the guidelines mark an important step forward there is still more to be done, according to the EGG. It makes two key recommendations:

1. That a European-wide tracking system be developed to monitor transmission of HIV-1 drug resistance in different geographical regions and/or risk groups.
2. That a major educational drive be undertaken to communicate both the value of resistance testing and the overall goal of an equal standard of care for people with HIV throughout Europe.

"Progress in technology and improvements in our understanding of HIV disease and treatment have increased the feasibility of resistance testing in routine clinical care," added Dr Miller. "Taking a lead from the world of microbiology, where antimicrobial resistance testing is routine, HIV-1 resistance testing may soon become standard practice in HIV treatment management, leading to better clinical and virological outcomes for all patients."

Source: EGG press release

U.S.A HIV treatment guidelines updated for adults and adolescents

An updated version of the Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, which includes revised recommendations for when to initiate anti-HIV therapy has been posted to the HIV/AIDS Treatment Information Service (ATIS) Web site:

http://www.hivatis.org

The Guidelines were developed by the Panel on Clinical Practices for the Treatment of HIV Infection, a joint effort of the Department of Health and Human Services and the Henry J. Kaiser Family Foundation. Initially published in 1998, the Guidelines were constructed as a "living document" and are updated by the Panel as new data emerge.

"Although antiretroviral therapy has provided extraordinary benefits to many patients, we know that we cannot eradicate HIV infection with currently available medications," says Anthony S. Fauci, M.D., director of the National Institute of Allergy and Infectious Diseases (NIAID) and co-chair of the Panel. "We also recognize that serious toxicities are associated with the long-term use of antiretroviral drugs. The new treatment guidelines provide patients and their doctors with evidence-based recommendations for initiating antiretroviral therapy that take into account both the benefits and potential risks of currently available treatment regimens."

The new Guidelines recommend considering starting antiretroviral therapy when an asymptomatic HIV-infected person's CD4+ T-cell count falls below 350 cells per cubic millimetre (mm3); previous Guidelines recommended consideration of therapy for asymptomatic patients with a CD4+ T-cell count lower than 500 cells/mm3.

For asymptomatic HIV-infected patients with CD4+ T-cell counts higher than 350 cells/mm3, treatment should be considered when the level of HIV in plasma is high [more than 30,000 copies per millilitre (ml) when using the branched DNA test, or more than 55,000 copies/ml when using the RT-PCR test]; previous Guidelines recommended consideration of therapy at lower levels of plasma HIV (10,000 copies/ml measured by branched DNA, or 20,000 copies/ml measured by RT-PCR).

The Guidelines continue to recommend antiretroviral therapy for all patients with the acute HIV syndrome, those within six months of HIV seroconversion, and all patients with symptoms ascribed to HIV infection.

The Panel stresses that the Guidelines should be considered as a tool to help patients and their physicians make individual treatment decisions based on the best available information, but that much remains to be learned about how best to treat HIV-infected individuals.

"The updated Guidelines recognize that we do not yet have the data we need to make definitive recommendations about the optimal time to start treatment," says John G. Bartlett, M.D., chief of the division of infectious diseases at the Johns Hopkins University Medical Center and co-chair of the Panel. "We highlight the uncertainty, allow for flexibility, encourage an individualized approach to treatment, and, at the same time, try to provide guidance."

The Guidelines also include new drug-specific recommendations. Two new entries are included in the "strongly recommended" category of anti-HIV drug treatments. One of these is the recently approved *[in the U.S.]* protease inhibitor Kaletra, which is a co-formulation of lopinavir and ritonavir. The other new entry is the combination of ritonavir and indinavir. These treatment options take advantage of the ability of ritonavir to boost the levels of other protease inhibitors, creating a potent anti-HIV combination. The protease inhibitor combinations are used along with combinations of certain nucleoside analogue reverse transcriptase inhibitors, which represent the "backbone" of anti-HIV treatments.

Also in the revised Guidelines is a section on the importance of adherence to therapy. "Extraordinarily high rates of adherence to an antiviral drug regimen are necessary to maintain control over HIV replication," says Dr. Bartlett. "HIV is very unforgiving in this regard. It is impossible to over-emphasize the importance of maximizing adherence once the decision is made to begin therapy."

Another important addition to the Guidelines is an updated section on the expanding scope of antiretroviral drug toxicities. "We are very concerned about a number of toxicities associated with the long-term use of antiretroviral drugs," says Dr. Fauci. "Particularly alarming is the alteration of fat metabolism that can emerge during treatment. We are seeing an increasing number of patients with dangerously high levels of cholesterol and triglycerides. The good news is that new anti-HIV treatments have dramatically improved the quality of life for many patients, and the incidence of AIDS and AIDS-related deaths has dramatically decreased. The bad news is that we now must find ways to deal with unanticipated toxicities, including the potential for premature coronary disease."

The updated Guidelines are available at:

http://www.hivatis.org

in two formats, a typeset version (PDF) and a Web version (HTML). Single copies can be ordered by calling 1-800-448-0440 (international callers may call 1-301-519-0459), or by sending an e-mail request to atis@hivatis.org.

U.S.A. Perinatal Treatment Guidelines Updated, January 24, 2001

The HIV/AIDS Treatment Information Services (ATIS) announces the release of the updated Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States guidelines.

The primary changes include:

- An expanded section on mitochondrial toxicity and nucleoside analogue drugs and issues in pregnancy. Recent data released by Bristol-Myers Squibb reported 3 maternal deaths due to lactic acidosis, 2 with and 1 without accompanying pancreatitis, in women who were

either pregnant or postpartum and whose antepartum therapy during pregnancy included d4T/3TC at the time of conception and throughout pregnancy who presented with symptoms and foetal demise at 38 weeks gestation.

- A new section on Preconceptional Counseling and Care for HIV-Infected Women of Childbearing Age has been added.
- An updated discussion section of the Antiretroviral Scenarios #1 and #2 and #4.

The updated guidelines are available at:

http://hivatis.org/trtgdlns.html

You can request a copy of the updated guidelines in hardcopy or have a PDF file sent directly to your email address through our easy on-line ordering system at

http://hivatis.org/request.html?list

8th Conference on Retroviruses and Opportunistic Infections

February 4 – 8, 2001. Chicago, IL

Differentiating within and between drug classes: Sometimes it's toxicity, sometimes its efficacy

Dr Graeme Moyle MD, MBBS, Chelsea & Westminster Hospital, London for NATAP

www.natap.org

The new DHHS guidelines include additions to the list of strongly recommended agents and nucleoside combinations but nothing has been removed from the list since the last major revision. The additions include 3 boosted PI regimens, low dose ritonavir (RTV) with either saquinavir, indinavir or lopinavir (combined tablets Kaletra). However, 2 unboosted PIs, nelfinavir and indinavir remain on the strongly recommended list despite inferior antiviral efficacy being observed in randomised clinical trials; nelfinavir being inferior to Kaletra, indinavir to efavirenz. Further efforts to compare the combinations most widely used were reported during CROI.

Are the nucleoside combinations different as backbones?

Studies form the dual therapy era suggested that, at least for the most widely used (and DHHS recommended) regimens of ZDV or d4T plus either ddI or 3TC the answer was no difference. Thus the choice between these backbones would be made on issues such as impact of future treatment options via resistance, frequency and severity of adverse effects, impact on body shape and convenience of administration with the third agent in the regimen. Evidence to clearly inform these debates are limited, but each approach has its pros and cons.

Data regarding body shape, for example, vary substantially between studies. In patients who have only received ZDV or d4T backbones, one study (consistent with previous data) found similar rates of fat loss and fat accumulation between these drugs [1]. Whereas results from a subset of patients drawn from a randomised study of d4T vs. ZDV based regimens (in combination with 3TC + indinavir) in individuals with substantial prior ZDV experience found similar efficacy and tolerability. However, in a cross sectional survey of 96 of the 170 randomised subjects, higher rates of lipoatrophy were found in those treated with d4T [2].

The reasons for the differences between studies remains unclear, and could relate to methodological issues, but raise the question as to whether prior ZDV use predisposes d4T recipients to lipoatrophy. Efficacy comparison between ZDV+3TC (n = 206) and d4T + 3TC (n = 101) or ddI chewable tablets (n = 102) (all with indinavir) were provided from the

naïve patients in the START study [3]. Overall the median baseline viral load (VL) and CD4 counts were 4.53 log10copies/mL (34,000 copies/ml) and 407 cells/mm3, and were similar between groups. At week 72, the proportions of available patients remaining on initial therapy with HIV VL <500 copies/mL were for ZDV/3TC 72% (48/67), d4T/ddI 69% (24/35), and d4T/3TC 80% (35/44) with no significant difference between groups (p > 0.20 for all comparisons). This suggests that these backbone nuke combinations each provide similar antiviral efficacy.

The main drawback to ddI use has been the mostly mild but relatively common gastrointestinal (GI) side effects observed with the chewable tablets and the need for separation from fat and protein containing meals. The recently approved EC formulation, which is thought to avoid these GI effects, was compared in a randomised trial of 138 treatment-naive patients to the older chewable tablet, each once per day, in combination with d4T and nelfinavir [4].

Median baseline VL levels (4.73, 4.59 log10 copies/mL, 54,000 vs 39,000) and CD4 counts (382, 381) cells/mm3 in the EC and tablet arms respectively were similar between groups. Mean HIV RNA levels over 48 weeks showed similar profiles for both regimens, with a slightly larger decrease in EC recipients (-2.62 and -2.35 log10c/mL for EC and tablet, respectively). CD4 increases were about the same in both groups. The tolerability data indicated that significantly more subjects discontinued for adverse events from the tablet regimen (20%) compared with the EC regimen (7%; p = 0.04), suggesting better tolerability the new regimen provides better tolerability. Previously reported data with efavirenz, nevirapine, indinavir and RTV boosted saquinavir all indicate that ddI EC does not need to be separated from the dosing of these agents.

In a separate trial ddI EC plus d4T was compared with Combivir (ZDV+3TC combined tablets) in an open-label, randomised study [5]. Data from 333 of 511 treatment-naive subjects with therapy through 48 weeks were analysed. Similar proportions of subjects on both regimens had VL <400 copies/mL at week 48 (ddI EC/d4T 57%, Combivir 55%) and <50 copies/mL (difference 0.2%). Median CD4 counts also increased similarly in both regimens. As these two combinations appear similar in antiviral efficacy the choice for each individual will be based on adverse events rates. Between the ddI EC/d4T and Combivir arms rates of all grades of adverse events reported were diarrhoea 54% and 56% (presumably mostly secondary to nelfinavir), nausea 21% and 35%, vomiting 13% and 18%, and peripheral neurological symptoms (all grade I-II) in 17% and 8%.

Discontinuations for adverse events were similar in number, occurring early in Combivir and later in the ddI EC/arm. Lipodystrophy events were not reported. These data suggest the choice between these combinations will be one of risk of mild to moderate peripheral neurological symptoms but better initial tolerability with ddI EC/d4T versus more nausea and vomiting with Combivir.

Once Daily Regimens

The number of potential or approved once daily regimens is gradually increasing making the arrival of routine once daily therapy increasing a reality. Data on FTC and tenofovir, new once daily NRTIs are included in other reports from this conference. Both efavirenz and ddI are approved for once daily use and interest is growing in using 3TC and abacavir as once daily drugs. A 24-week comparison confirmed the feasibility of once daily 3TC [6]. This prospective, randomised, trial compared the efficacy and tolerability of a switch to 3TC 300 mg QD vs. continued standard dosing of 3TC 150 mg BID in subjects with virologic suppression <400 copies/mL for >3 months) on >6 months 3TC, d4T and indinavir or nelfinavir. Of 81 dosed patients, 78 subjects completed the study. Not surprisingly, a high rate of virologic suppression (<400 copies/mL) as sustained through 24 weeks by both regimens (once daily 95%, BID 90% by ITT analysis). For <50 copies/mL 82% of subjects on QD regimen had VL and 81% on BID regimen remained undetectable. No virologic failures (for some obscure reason defined as >1265 copies/mL on 2 separate occasions >2-4 weeks apart) occurred and CD4 increases were similar for both dosing regimens. Both dosing regimens were well tolerated with no drug-related serious adverse events were reported.

Given these and other data it is not surprising that data from two non-comparative evaluations of once daily ddI + efavirenz with 3TC [7] and FTC [8] reported impressive levels of viral suppression and tolerability.

Efficacy differences between NNRTIs?

Concerns regarding liver toxicity with nevirapine had been raised from the FTC studies (see my previous NATAP report from this conference). A further presentation at the conference raised concern that this agent may also have lower efficacy relative to efavirenz. This report was a retrospective analysis of 1932 patients given their first NNRTI regimens containing either nevirapine (n=1202) or efavirenz (n=730), derived from the large EuroSIDA cohort [9].

EuroSIDA is a pan-European, clinic-based project that collects data from 64 clinics. Patients who began a regimen with nevirapine or efavirenz after July 1997 were studied. Virologic failure was defined as 2 consecutive VL >500 copies/mL at least 6 months after starting the regimen. Baseline characteristics were similar with a viral load of 3.7 vs. 3.9 log10 copies/mL, for EFV and NVP groups, respectively), and baseline CD4+ cell count (269 vs. 266 cells/mm3). Prior AIDS diagnosis was slightly more common in EFV recipients 41% relative to 34%of NVP recipients. Only 5% of patients were NRTI-naive, and over 75% had received at least 3 NRTIs, while almost half of the patients had received at least 2 protease inhibitors (PIs).

Factors associated with clinical or virologic failure included number of previous NRTIs or PIs, CD4+ cell count nadir or previous AIDS diagnosis, baseline viral load and number of NRTIs in the regimen. Virologic rebound at 12 months were 48% and 65% for EFV and NVP, respectively. The chance of virological rebound or clinical progression was significantly lower with EFV regimens. The relative hazard (adjusted for baseline characteristics) of viral rebound at 12 months was 0.57 (CI 0.47-0.69, p=0.001) representing a 43% lower chance of this event relative to NVP. For clinical progression the relative hazard was 0.49 (CI 0.33-0.74, p=0 .0005), a reduction of 51% of progression. A randomised comparison of these drugs in treatment naïve patients is currently recruiting and may answer the issue as to relative efficacy in these

circumstances. A direct comparison in NRTI, PI experience patients, based on these data, is urgently warranted.

NNRTI versus PI in initial therapy

The DPC-006 study established efavirenz as a first-line NNRTI option demonstrating superiority of 8-hourly dosed indinavir both in combination with ZDV and 3TC. Longer-term (144-week) follow-up data indicated that these advantages over indinavir, and viral suppression, are sustained. Only 8% of patients randomised to EFV failed to achieve viral suppression to <50 copies/mL in the study with the rebound rate being 8% by 52 weeks, with a further 7% between weeks 53 and 96. Incomplete suppression rates of approximately 16% and rebound rates of 16% by week 52 and a further 6% between 52 weeks and 96 weeks occurred in the IDV arm.

After 96 weeks with fewer patients available for analysis, rebound occurred in 3.5% of EFV and IDV patients. Using a mathematical model based on rebound rates in years 1 and 2 it was estimated that the median time to virologic rebound with the EFV based regimen will exceed 6 years [10]. If the lower rate of rebound in years 3 were considered, it is possible this estimate of durability may have been longer.

Data from the COMBINE Study comparing NVP with nelfinavir (both dosed BID with Combivir) in a randomised, open label study of 142 naive patients reported 36-week data at the conference [11]. One difficulty with interpretation of the results of this study lies in modest baseline differences, which occurred by chance at randomisation, but may have favoured the NVP arm. About 40% in each arm were HIV-infected by IVDU. This may have affected adherence, as adherence to NFV was less than to NVP. It's also possible that methadone or illegal drug use may have affected blood levels of HIV drugs. As well, the percentages of heterosexuals were 31% NFV vs 20% NVP, and homosexuals were 18% NFV vs 37% NVP.

Data on the poster on a selected subgroup of 15 patients on NFV who had <20 copies/ml showed good blood levels. Indeed, 10 patients did not return for follow-up after randomisation, 8 in NFV and 2 in NVP arms, this difference affecting the ITT analysis in the NFV arm by >10% but by <5% in the NVP arm. At 1 month into study 95% adherence was 59% for NFV vs 75% for NVP (p=0.03). Other baseline characteristics included a mean CD4 count of 359 (range 10-908) cells/mmm3 and median viral load of 4.78 (range3.2-6.2) log10 —about equal in both arms.

In the 36-week ITT analysis, 55.7% of the NFV versus 70.8% of the NVP recipients had VL <200 copies/mL (p=0.06). The on-treatment analysis showed 78% in NFV arm versus 83.7% in the NVP arm were <200 copies/mL (p=0.50). Using a <20 copies/mL assay, 38.6% in the NFV arm versus 66.7% in the NVP arm achieved this level of suppression in an ITT analysis (p<0.001). The OT analysis to <20 copies/mL showed 56.1% in the NFV arm versus 79.6% in the NVP arm (p=0.02). There were significant numbers of discontinuations due to side effects in both arms, 13/70 in NFV arm and 16/72 in NVP arm including several discontinuations on NVP due to hepatotoxicity (5/72), and due to NFV GI symptoms (10/70). Given the problems with these data it is difficult to say this study represents the final word in comparison between these two drugs. However, as both NVP and NFV are increasingly less common treatment choices amongst HIV clinicians, the definitive study is unlikely to be done. In the ITT analysis of patients with >100,000 viral load at baseline, 15.4% (4/26) taking NFV vs 61.9% (13/21) taking NVP had <20 copies/ml (p=0.001). 53% (14/26) for NFV vs 71% (15/21) had <200 copies/ml but this was not statistically significant (p=0.22).

Booster PIs outshine standard dosing: Kaletra

The combination of ritonavir 100mg bid with other PIs is increasingly viewed as the best way to use these agents, reducing pill load, boosting trough values albeit sometimes at the cost of (mostly) modest lipid increases. The co-formulation of lopinavir and ritonavir is the most recent example of this approach. Unlike boosted saquinavir and indinavir, this combination has the drawback of requiring dosing with food. The key trial for the approval of lopinavir/ritonavir (Kaletra) is a double blind, randomised trial of twice-daily stavudine/lamivudine plus either twice-daily lopinavir/ritonavir or 3-times-daily nelfinavir (changed to twice daily after 24 weeks) in patients essentially naive to antiretroviral therapy [12].

The study involved 653 patients showed superiority for the Kaletra arm over NFV, which became most evident at week 36 and 48 time-points. At 48 weeks, VL was <400 copies/mL in 75% of patients in the lopinavir/ritonavir arm and 63% of those in the NFV arm (P < .001) and <50 copies/mL in 67% and 52% of these arms, respectively (P < .001). The analysis presented at this conference looked at the time to treatment success defined as <50 copies/mL. The drawback of this analysis was that the <50 copy assay was not used on samples until week 24. At this time-point approximately similar proportions, 65% vs. 60% (p= not significant) of patients had VL <50 copies/mL. Amongst week 24 incomplete responders (>50 copies/ml at week 24) who remained on study, however, 88% of lopinavir/ritonavir-treated patients subsequently responded whereas only 41% of NFV patients subsequently achieved <50 copies/mL (P < .001).

Consistent with a similar analysis from the DPC-006 study with EFV, time to VL <50 copies/mL took longer in patients with baseline VL above100,000 copies/mL. Differences in the performance of the two drugs was most evident at this levels with 84% of patients randomised to lopinavir/ritonavir, compared with 60% of those on NFV eventually responding. These data also show that some individuals take longer than 24 weeks to reach <50 copies/ml. In an analysis using data from both treatment groups, patients with baseline <100,000 copies/ml were compared to those with >100,000 copies/ml. Patients with lower baseline viral load achieved <50 copies/ml more quickly than those with higher viral loads (p<0.001), regardless of whether patient received NFV or Kaletra.

However, there was a difference between NFV & Kaletra in terms of getting below 50 copies/ml if baseline viral load was >100,000. In the Kaletra group, similar proportions of patients with VL >100,000 copies/ml at baseline (84%) or >100,000 (85%) reached <50 copies/ml. In the NFV group, a significantly lower proportion of patients with VL >100,000 copies/ml (60%) than those with <100,000 copies/ml reached <50 copies/ml. People with higher baseline viral load can take longer to reach <50 copies/ml. Within each treatment group this was reflected. Ultimately, 85% for Kaletra vs 71% for NFV ever achieved <50 copies/ml, and a difference between

the two arms was not statistically seen until week 24. Abbott suggested week 48 as a more appropriate time-point to evaluate I reaching <50 copies/ml.

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Intermittent versus continuous HAART

Paul E. Sax, M.D. for thebody.com

A strategy of interrupted therapy — dubbed "structured intermittent therapy" — gained a major imprint of respectability at this past summer's International AIDS Conference in Durban when Anthony Fauci cited his group's preliminary work in this area. Numerous other terms have been applied to this practice, including "structured treatment interruption," "strategic treatment interruption," and "supervised intermittent therapy", but the basic principal underlying all of them is that antiretroviral therapy need not be continuous. In these two posters, Mark Dybul from Tony Fauci's lab presented their ongoing work in this area.

In the first poster [1], the question posed was, "Can 50% less antiretroviral therapy given as short-cycle 'structured intermittent therapy' maintain suppression of viral load to reduce cost and toxicity of treatment?" Patients were eligible to join the study if they had CD4 cell counts >300 and viral load <500 for more than six months, and had a viral load of <50 copies at the time of screening. The treatment strategy planned was seven days on/seven days off treatment for 24 months or until treatment failure (viral load >500 twice or CD4 decline by 25% or more) ensued.

At entry, all 10 patients were receiving the same antiretroviral therapy, which was d4T/3TC/ritonavir/indinavir. At the end of 3-11 months of follow-up, 8/10 maintained a viral load <50 during the course of study. One patient had a brief virologic rebound when he came off treatment for 10 days; a second patient failed to resume treatment after three weeks, and the viral load increased to 20,142 copies/mL. Both patients achieved virologic suppression when they resumed treatment. In the entire group, CD4 and CD8 counts did not change.

An analysis of viral reservoirs checking for amount of proviral DNA and replication competent HIV both pre and post starting the intermittent treatment cycles showed no apparent increase in the reservoir. Furthermore, no decreased susceptibility to antiretroviral agents was detected when cultured virus underwent resistance testing.

Based on these preliminary data, the investigators concluded that it may be possible to safely decrease the amount of antiretroviral therapy administered by 50% without untoward effects on virologic control or immune status. Such a strategy would be particularly appealing in resource-poor settings or if it were shown to be associated with lower cumulative drug toxicity. Given the small size of the sample presented here, however, this particular approach awaits further follow-up on a larger number of patients.

The group's second paper [2] employed a different study design: taking patients on suppressive antiretroviral therapy and randomising half to continue that treatment, and half to begin a schedule of intermittent treatment consisting of one month off therapy followed by two months on. To be eligible, patients had to have a CD4 cell count >300 and a viral load <500 for greater than three months, as well as a viral load <50 at the time of study entry. The primary endpoint was the time to viral load rebound or CD4 decline, with secondary endpoints CD4 and CD8 t-cell mediated HIV-specific immune responses.

Although a total of 70 patients will ultimately enrol, preliminary results on the 47 thus far participating were presented. At baseline, the patients randomised to intermittent versus continuous therapy were similar regarding the mean CD4 nadir, CD4 count at study entry, and peak pre-treatment viral load. For the fifteen patients in the intermittent therapy group for whom three to six cycles of interruption had been completed, four different patterns were observed:

- 3/15: each treatment interruption was associated with a 0.5 log or greater reduction in peak viral load
- 2/15: each interruption had a .5 log or greater increase in viral load
- 5/15: interruptions had variable viral load rebounds
- 4/15: rebounds were similar each time

Patients who were in the SIT group had a similar number of measurements >50 copies/mL ("blips") during treatment as did the continuous therapy group. CD4 cell counts did decline during the treatment interruptions, but these rebounded to baseline during resumption of therapy. Of some concern, one (out of five) patients on efavirenz who was in the intermittent treatment group developed genotypic and

phenotypic resistance to this agent.

Based on these preliminary results, the investigators concluded that there was no clear pattern of virologic rebound in these chronically infected patients who undergo this particular schedule of treatment interruption. While the stable CD4 cell counts overall was a promising sign, even the one patient who developed NNRTI resistance during the study raises concern about the potential for resistance with intermittent therapy. This may be particularly problematic for drugs with long elimination phases, such as efavirenz. The bottom line from these two studies of intermittent treatment is that STI remains a strategy under investigation, and cannot yet be endorsed for routine clinical practice.

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Source:
www.thebody.com

The clinical correlates of protease inhibitor regimen failure

Richard Alan Elion, M.D. for thebody.com

Despite the progress of the treatment of HIV infection, we are still encountering treatment failures. These "failures" can be defined in different ways, beginning with either an intolerance to HIV medications or the development of widespread resistance and the subsequent failure of the medications to abolish viral replication. Deeks in earlier work described how the common clinical picture of patients with persistent viral replication, intermediate viral loads ranging as high as 70,000 copies though the upper limit, and stable CD4 counts is not thoroughly understood. Rather, there was no obvious immunologic decline despite viral replication. This became known as a "disconnect" or "discordancy" between the viral control and immune decline. There are numerous theories for this discordancy ranging from viral mutations that are resistant to our medications to different viruses with different shapes and activity that are less antagonistic or virulent to our immune system. Chaisson et al. (abstract 429) reported from their cohort in Baltimore that continuing treatment despite virologic failure resulted in higher CD4 counts than in patients who discontinued therapy. We are creating an unsteady truce between viral suppression, the selection of different viruses, and immunologic control.

This trial was a retrospective observational study of 485 patients at San Francisco General Hospital, 302 of which had confirmed virologic failure. These patients had median CD4 counts of 124 and median HIV RNA of 4.81 log (approximately 75,000 copies/mL) before the initiation of a protease inhibitor. At the onset of subsequent virologic failure there was a probability of clinical progression of 18% at two years and 41% at four years. This progression was independently associated with a return of viral load to the vicinity of the original viral set point before the initiation of therapy and with a low CD4 nadir prior to therapy as well. Apparently, the progression may have been related to the strength of patients' original responses as measured by the level of viral load or CD4 count at the time of therapy initiation, and interestingly, was not related to the highest point of viral load achieved.

Deeks et al. concluded that clinical progression is unfortunately common after four years of continuous virologic failure and could be predicted by the original set point of virologic control and the low point of immune decline as measured by the nadir of the CD4 count. However, 59% of the patients had still not progressed after four years of clinical failure, giving hope to the notion that maintaining a failing regimen as reflected in persistent viral replication may be a viable strategy — as long as some measure of virological suppression can be maintained. How much suppression is enough has not been clearly determined; this will drive future development of novel strategies for these long-term, slowly progressing viral failures. We may be creating persistently replicating but less-virulent viral strains. It is hopeful to know that we are buying time, but it is not clear how much time we are buying. There is hope that a combination of new approaches involving treatment interruptions (see abstract 292) and new therapies could create new options that would result in greater clinical stability.

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Source:
www.thebody.com

Viral load "blips" and eventual rebound

Cal Cohen, M.D. for thebody.com

During the past few years, it has been repeatedly shown that any regimen that gets viral loads down to below 50 copies is clearly more durable in maintaining viral suppression than those regimens that do not achieve this degree of viral suppression. However, it has also been noted that some people who have a viral load below 50 will also, occasionally, have a viral load above this level. There have been a few groups who have helped define the impact for those whose viral loads go transiently above 50 copies, after viral suppression was achieved on a regimen. This pattern has been commonly referred to as a viral load "blip."

For this study, a group of European researchers monitored the viral loads of about 2,500 people who were on standard triple regimens. The group monitored the outcome for those who, while on antivirals, had a viral load below 50 copies on two consecutive tests. They defined viral rebound, or failure, as a viral load over 500 copies. They examined the rates of failure in those whose viral loads went over 50 copies but were less than 500 copies — this is the range defined as a "blip" in this study. Most of those who had one reading in this range had viral suppression below 50 copies on the next reading, although about 20% did rebound on a follow-up

reading. They then examined the number of consecutive readings in this low range, to see if that was important in predicting who would re-suppress versus those who would rebound. In fact, the longer someone had a viral load between 50 and 500, the more likely there was eventual rebound. Those who had a sustained viral load between 51-500 were five times more likely to eventually go over 500 copies than those who stayed below 50 copies on all readings. Moreover, they noted that there was a trend showing a difference in the rates of rebound for those whose viral loads were between 50-100 copies, versus those whose "blip" was between 100-500 copies, as the group with the lower level blip were more likely to re-suppress.

These results confirm what we might have predicted from prior work done in defining the keys to successful suppression. Overall, if HIV can grow in the presence of antiviral medication, it can eventually create resistance to these medications and this leads to higher and higher viral load levels — heading back toward the patient's pre-treatment set point.

For reasons that remain unclear, there seems to be ongoing success for those people who have viral loads below 50 copies, which differs from the success rates for people with a viral load even just a small amount over 50 copies. This study suggests that both the duration and height of the "blip" are helpful in predicting how likely it is that HIV will stay suppressed despite a blip. However, it also emphasizes the point that, while one blip at a low level may have little impact, higher-level blips, or sustained low-level viral loads, may be a precursor to eventual viral escape. Re-emphasising medication adherence is certainly warranted as one first step to prevent this outcome.

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Source:
www.thebody.com

Interaction between Garlic and Saquinavir and underreporting of alternative treatment use

Simon Collins for HIV i-Base

Steven Piscatelli who has previously reported the issue of interactions between both St Johns Wort and Milk Thistle with protease inhibitors presented results from a PK interaction study between garlic supplements and saquinavir in 10 HIV-negative volunteers.

Baseline drug plasma levels were measured after 1200mg saquinavir (SQV) had been given three times a day with meals for three days. Garlic capsules (strength not specified) were then given twice daily with meals for days 5-25. Saquinavir was added for days 22-24. At day 25 AUC and Cmin and Cmax levels of saquinavir were reduced by approximately 50%. It was also noted that three-day saquinavir levels remained approximately 60-70% below baseline even following a 3-week washout period of all drugs and that garlic supplements may produce a prolonged induction of SQV metabolism. [1]

A second study showed that alternative and supplementary medications are often not recorded in medical notes. 324 patient interviews (approximately half the patients at University of Cleveland) between April-July 2000 showed that 267 (82%) confirmed ever having used a total of 567 different forms of alternative therapies. At the time of interview, 134 patients were using 333 different alternative therapies. Therapies unlikely to interact or affect HIV treatment (such as teas or massage) accounted for 25% of this reports. 40% concerned micronutrients and vitamins. 26% related to herbal supplements such as echinacea, St. John's Wort, and cat's claw. Protein supplements and anabolic steroids represented 21 (6%). Most patients (59%) stated they had informed their physicians about their alternative therapy use, but this information was registered in the patients' chart only 13% of the time. Physicians consistently documented use of anabolic steroids but recorded the use of other forms of alternative therapy variably (0—20%).

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C O M M E N T

It should not be forgotten that garlic is also a common food item. As such there is the potential for drug interactions such as the one described above occurring simply through dietary intake of such foods. A common observation amongst HIV-infected persons receiving ritonavir is of increased gastrointestinal upset when taking garlic supplements or eating food containing garlic. A previous study (ref) reported that garlic did not influence the pharmacokinetics of ritonavir. Ritonavir may, however, alter the levels of some constituents of garlic thereby increasing toxicities. The effect of ritonavir on garlic has yet to be investigated.

Solid Organ Transplant in HIV/hepatitis co-infected patients

Simon Collins for HIV i-Base

HIV-positive patients have previously been excluded from liver or kidney transplant operations due largely to concerns of allocation of limited resources for patients assumed to have a poor prognosis and concerns of accelerating HIV progression from use of immunosuppressive drugs. The wide extent of co-infection in both Europe and the US has been well documented and liver failure is now amongst the highest causes of HIV-related mortality and morbidity. It was therefore encouraging to see a poster reporting eight cases

of liver transplants carried out at Kings College, London between 1995-2000. [1]

Four patients had end stage liver disease (ESLD) related to HCV (3 with haemophilia A). Two patients had acute liver failure; one related to HBV, one to non-A non-B. One had chronic ESLD due to HBV.

All patients survived the immediate post-transplant period, although the four patients with HCV died from complications from recurrent HCV infection 3-25 months post transplant despite use of interferon alpha plus ribavirin treatment in two of the cases.

The four patients with HBV all survive with good graft function at 33, 13, 3 and 1 month post transplant. HBV is treated with lamivudine (3TC) and hepatitis B immunoglobulin. No HIV complication have been reported in these patients who continue HAART treatment with undetectable viral loads and CD4 counts >200 cells/mm3.

As improved treatments for HCV and HBV continue to develop, often incidentally with overlapping activity against HIV, the study notes that HIV-infection should not be seen as an absolute contraindication for liver transplantation.

These results were supported in a report of five patients treated at the University of California, San Francisco with ESLD (n=1) or end stage kidney disease (n=4). The patient coinfected with HCV required a re-transplantation (small for size graft lesion) and responded to interferon alpha plus ribavirin treatment. Two episodes of reversible kidney rejection (plus one currently being treated) were reported. All patients are alive at a median of 138 days (62-216 days) post transplant. [2]

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HIV and Women – overview from the 8th CROI

Polly Clayden, for HIV i-Base

At first glance this conference showed an impressive range of sessions and posters dedicated to women's HIV care. Further examination however revealed very few studies actually addressing women-specific research, independent of their role in reproduction. As usual there were challenging issues of semantics - HIV-infected and 'normal' women being our conference favourite.

Many studies reported and planned for the developing world demonstrated ever more complex ways of not treating women's own health – vertical transmission prophylaxis for mothers, vertical transmission prophylaxis for babies, breastfeeding prophylaxis for mothers, breastfeeding prophylaxis for babies…Rarely was this issue highlighted - after an update on the HIV 012 where concerns about nevirapine resistance were raised if a woman 'presents with another pregnancy'. Although we were pleased to hear a question asked about the implications of NNRTI resistance when HAART is introduced in this population, it didn't cause much of a stir.

In addition to this, as is customary, two so-called 'special' patient groups were grouped together in sessions entitled Maternal-Foetal transmission of HIV-1 Implications for Care of HIV Affected Women and Children and HIV Infection in Women/Pediatrics (score out of 10 for the latter symposium – 7 presentations on children, 2 on pregnancy and one on women alone). Although not quite as puzzling as the recent Glasgow conference which combined women, children and IDVUs (why?) this was enough to provoke the comment from one activist who remarked 'Why not men and mice?'

HAART use during pregnancy

Mary Glenn Fowler from the CDC (Center for Disease Control) presented an overview of the most recent research concerning perinatal transmission both in the US and internationally entitled Update on Prevention of Mother-to-Child HIV Transmission: US Successes, International Challenges [1]. She reported findings from recent studies showing that appropriate use of HAART for a woman's own health during pregnancy has dramatically reduced transmission rates to less than 1%. Trends in antiretroviral use have changed greatly as demonstrated in data from PACTG 367 reporting 78% women using complex therapy in pregnancy in the US between January 1998 and May 2000 – including 42% using PI-containing regimens.

Elective C-section increasing

Dr Fowler reported C-section rates for HIV positive women in the US of 40-45% in the US in 1999 and 2000 and 78% in Europe as reported by The European Collaborative Study [2]. Several posters looked at this trend in detail, including the CDC study which showed how the US rate had risen from 19% in 1994 to 44% in 2000 and that it had doubled from 1997 [3]. The extent to which this intervention is used, particularly in Europe was surprising as no data to date have demonstrated any additional benefit to be gained from using elective C-section among women using potent antiretroviral therapy during pregnancy.

One report concluded that 'Future studies are necessary to determine whether there is an incremental benefit of C-section delivery in women receiving prenatal ART with successful HIV suppression' [4]. As transmission rates continue to be as low as less than 1%, regardless of mode of delivery, it seems unlikely that these data will be forthcoming.

Some groups still at risk

Despite great advances for the majority in the developed world, a small group of women still slip through the net. Dr Fowler explained that these included - late presenters with no prenatal care, women not perceived to be at risk and therefore not offered testing, women who were non-adherent although prescribed antiretrovirals and women experiencing treatment failure.

Reports from the MIRIAD study showed the feasibility of offering rapid testing at delivery to late presenters and substantial US funds ($10,000 per year) are being directed at programmes targeting states with high HIV prevalence.

Different picture in resource-poor countries

Dr Fowler went on to speak about the ever-growing contrast between north and south and how obstacles in the developing word still remain daunting. Adolescent infection is increasing disproportionally among girls in Africa. For example in Kisumu, Kenya 8% of 15 year old girls are HIV positive, increasing to 30% by age 17 and 33% by 19 years, whereas infection rates for teenage boys in the same region are still comparatively low (8.6% by age 19).

Because of HIV, a projected figure of 200 per 1000 young children in Zimbabwe will die before they are 5 years old. Among breast-feeding populations about one third of transmissions occur through this mode of transmission. Risk factors include – younger maternal age, lower parity, post-natal seroconversion, duration of breast-feeding, maternal CD4, viral load in breast milk, nipple lesions, mastisis and infant oral thrush. There appears to be a continued risk throughout the duration of breast-feeding but there is an indication that most transmission appears early [5,6]. Risk of transmission is about 0.7 per month in the infant's first year and 0.3 per month in the second.

Findings from the HIVNet 012 trial showed 16% and 24% of infants infected in their first year in the nevirapine and AZT arms respectively [7]. Over twelve studies are currently investigating interventions to reduce breast-feeding transmission, these include infant prophylaxis during breastfeeding, passive immune therapy is being studied in Uganda, exclusive breastfeeding in South Africa (mixed feeding appears to by associated with the highest transmission rates [8]) and abrupt early weaning in Zambia. Despite being reminded of Dr Ruth Ndati's chilling report in which breastfeeding HIV-positive women in Kenya were found to have a 3-fold increase in their mortality rate [9], and that uninfected children born to HIV positive mothers also have a higher infant mortality rate, no planned studies were reported that focus on the issue of maternal health.

Nevirapine resistance

A further update was presented from the HIVNET 012 trial, in which treatment naïve Ugandan women received prophylaxis nevirapine to prevent vertical transmission, followed by a dose to the baby [10]. Dr Susan Eshleman first presented resistance data from this study at the 7th CROI a year ago [11]. Last year's findings showed the K103N primary NNRTI mutation present in plasma of 20% of women studied, after only one dose of nevirapine. Further observations from this ongoing trial reported 45% of infected babies also having nevirapine resistance. In addition the mother-infant pairs were found to have differing genotypes – the Y181C being the most common mutation among the infected infants– suggesting that the babies' resistance may be selected independently to the mothers'. Unsurprisingly the presence of resistance was most prevalent in samples from women with high viral load and low CD4 count at the time of labour. Although a question from the audience at this meeting raised the point 'Are you possibly underestimating resistance, as you are not detecting it in women of low viral load?'

New findings presented also included the worrying report of one case of nevirapine resistant virus being transmitted from mother to baby via breastfeeding. In the context of ongoing and planned trials to prophylax both mothers and babies with nevirapine alone, this news should raise additional concerns. Dr Eshleman's presentation concluded with the report that 'nevirapine mutations appear to fade from detection in women and infants over time, but it is still unknown whether nevirapine would be effective when she presents with a subsequent pregnancy…'

In addition a poster reported genotypic resistance analysis in women participating in PACTG 316 with viral load above 400 copies/ml [12]. This study evaluated the effect of adding single-dose of 200mg nevirapine to standard antiretroviral therapy/prophylaxis to the mother at time of labour and 2mg/kg to the baby within 72 hours of birth vs.placebo, to further reduce transmission (see below). Plasma samples from 104 women were analysed both from delivery and 6 weeks postpartum. Of the 46 women who had received study drug, 5 (11%) had detectable mutations associated with nevirapine resistance after a single dose. Nucleoside and PI resistance mutations were also detected, mutations were most frequently observed in women with lower CD4 counts using PI-containing regimens.

Results from PACTG 316

Results from the PACTG 316 were presented for the first time as a late breaker at this meeting [13]. Describing the sample size hypothesis, principle investigator Dr Alejandro Dorenbaum explained that when they designed this study they had anticipated a 5% perinatal transmission rate. So to achieve 80% power to detect a 50% reduction (from 5% to 2.5%) they required a sample size of 2009 (1808 plus 10% loss rate). However due to the overall low transmission rate the trial was stopped on recommendation of their DSMB after 1267 mother and infant pairs had been randomised to receive nevirapine or placebo.

Of the participating women, none had used NNRTIs prior to enrolment. 1% received no treatment in addition to the nevirapine; 23% received AZT monotherapy; 28% received AZT and 3TC and 41% PI-containing combinations. 49% of women had viral loads below detection (less than 400copies/ml) at delivery. There was no significant difference between the nevirapine and placebo arms (9 and 8 transmissions respectively) and the overall rate of transmission was low - 1.5%.

This provoked some interesting reactions, including a mainstream journalist overheard in the pressroom calling his news desk with the news that 'You know that wonder drug nevirapine? Well it doesn't work!' Against a background of fully suppressive HAART, any additional benefit to be gained by adding nevirapine at delivery would be unexpected, it is hoped that women in the developed world can expect to receive optimal therapy in this setting.

However with no treatment or mono or dual therapy and with a larger sample size, using nevirapine in this way would certainly be expected to add benefit to transmission rates, resistance not withstanding. Dr Dorenbaun concluded that 'A woman should be treated in the best possible manner for her own disease (author's note -a message that deserves emphasising) and additionally pregnant women are strongly recommended to initiate therapy to prevent transmission, independent of their disease process.'

Important factors in transmission

Several posters looked at factors associated with perinatal transmission. These included an additional report from the PACTG 316 looking at PI concentrations in cord blood [14]. Although the use of protease inhibitors is growing during pregnancy few data are available measuring PI concentrations after their use. In this study cord blood plasma samples were collected at delivery from 68 women using PI-containing regimens. 38 women received nelfinavir, 21 indinavir, 8 saquinavir, and 6 ritonavir (4 women received more than one protease inhibitor).

The last maternal dose was administered a median of 12.2 hours (range 0.67-40.9) before delivery for the 26 women for whom this information was available. PI concentrations were undetectable in 53 (78%) of the samples. Of the 15 women with detectable cord blood concentrations, 14 were using nelfinavir and 1 ritonavir. Cord blood PI concentrations were revealed to be extremely low after maternal treatment during pregnancy. The investigators suggested that this could reflect lack of dosing during delivery, poor maternal PI absorption and/or poor placental PI transfer, and that it is unlikely that maternal PI use provides post exposure prophylaxis to the baby immediately after birth. These findings also highlight a notable take home message to those caring for HIV-positive pregnant women ie the importance of remembering to take their meds during labour.

Seventy-five percent of infants (born to untreated mothers) exposed to maternal HIV infection are protected from in utero and perinatal transmission by mechanisms that are so far incompletely understood. When transmission does occur, non-syncytium inducing (NSI), M-tropic HIV-1 is most commonly involved. CCR5, a chemokine receptor, serves as a co-receptor for NSI/M-tropic HHIV-1 and may be a necessary co-receptor for sexual, parenteral and vertical transmission. Unlike adults, full term foetuses express a naïve (CD45 RO negative, CCR5 negative) immunophenotype on their PBMC, which is not thought to be susceptible by NSI/M-tropic, CCR5-utilising virus.

Dr Karen Beckerman's group examined the hypothesis that the bacterial infection, chorioamnionitis and preterm delivery could render a foetus susceptible to HIV infection via immune activation-associated induction of CCR5 expression by foetal PBMC [15]. Paired maternal and placental cord blood samples were collected from 12 pregnancies, obtained after delivery by elective C-section (n=3), vaginal delivery (n=3) or choirioamnionitis (n=6). Cells were then analysed for surface expression of CD4, CD25, CD45RO, CD69, CXCR4 and CCR5. They found that among foetuses experiencing no labour (C-section) or vaginal deliveries CD45 RO and CCR5 expression were considerably lower than in adult controls.

The investigators concluded that chorioamnionitis and preterm delivery are associated with significant activation of a foetal immunophenotype that predicts increased susceptibility to M-tropic/R5-utilising HIV-1. And they speculated that 'The protection of foetuses experiencing no labour or normal labour, from HIV-1 infection may be associated with the naïve, CCR5 negative immunophenotype observed in the peripheral immune compartment'. Since chorio generally affects 10-20% of deliveries Dr Beckerman recommended 'Very active management of labour'.

Transmission has been reported to occur occasionally even at very low maternal viral loads. One poster reported findings from a large meta-analysis combining data from seven European and US studies [16]. Out of a total of 1,202 women there were 44 cases of vertical transmission where maternal viral load was less than 1000 copies/ml at the time of or close to delivery. Of these the rate was only 8 out of 834 (1%) for women receiving treatment during pregnancy and/or delivery as oppose to 36 out of 368 (9.8%) receiving no treatment. Although this study demonstrates a vast reduction in transmission rates (90%) conferred by the prophylaxis effect of treatment, more importantly it makes a strong case for use of fully suppressive therapy for pregnant women particularly at the time of delivery regardless of viral load.

Impact of pregnancy and menopause on CD4 count

Studies have shown that CD4 counts are higher and viral load levels lower in HIV-positive women than HIV-positive men. This is speculated to be due to levels of reproductive hormones, which differ by gender and change throughout a woman's life. Dr Danisman and colleagues' report investigated the impact of pregnancy and menopause on CD4 counts in 382 HIV-infected women with a known interval of seroconversion [17].

They found that CD4 count dropped during pregnancy but increased again to pre-pregnancy levels after delivery. Although their numbers of post menopausal women were small (17 at the time of analysis), this group had lower CD4 counts 3 years after seroconversion than premenopausal women (333 and 399 cells respectively, p=0.09 after controlling for age).

The investigators concluded that this effect '…may be a result of changes in levels of reproductive hormones. Since levels of reproductive hormones also differ between men and women, this may explain gender differences in CD4 counts'.

'Hard drug use'

A WITS (Women and Infants Transmission Study) prospective study examined the effects of 'hard' drugs on markers of HIV progression in a large group of 1148 women enrolled between 1989 and 1995 (and therefore pre-HAART) [18]. The women were interviewed about their drug use, which was self – reported and also measured using periodic urine toxicology tests. The correlation between self-report and urine toxicology was good and hard drug use was defined as cocaine, crack, heroin, methadone and any injection drug use. 40% of the group studied reported drug use and differences in viral load and CD4 count were compared to non- users.

No difference in mean CD4% were found at baseline between the two groups, but users were found to have a higher mean viral load. In multivariate, longitudinal analyses, hard drug use was not associated with higher averages of either CD4% or viral load. The investigators concluded that hard drug use '…did not appear to affect immunological or virological parameters in this cohort of HIV-infected women and may not exert a "co-factor" effect upon disease progression.'

Genital compartment issues

Dr Sherlock and colleagues from British Columbia evaluated the reproducibility of vaginal and cervical viral load

measurements. The investigators wanted to ensure that these measurements are reproducible before using them to draw any conclusions [19]. A group of 14 HIV positive women were enrolled in a study of menstrual variation in viral load and followed over 2 menstrual cycles. Plasma, cervical and vaginal viral load samples were taken at initial and follow-up visits.

Their analysis of paired measurements showed good reproducibility for same site samples. The paired cervix/vagina measurements showed moderate correlation only; this was thought to be likely to be due to the high rate of negatives in those pairs. Standardised sample collection and modification of the Roche RNA extraction method allowed reproducible measurement of genital viral load.

With semen, drug-selected HIV-1 genotypes differing from those that are dominant in the blood plasma have been frequently observed. In women there are limited data on whether the genital tract may also be a compartment for differing drug-selected variants; Dr De Pasquale's group investigated this phenomenon [20].

7 HIV-positive women on failing antiretroviral therapy and 3 drug naïve women were studied; all had detectable viral loads in plasma and vagina or cervix. Resistance mutations selected by the failing drugs were found to be present in each compartment, 5 of the 7 women on failing therapy had different mutations in cervico-vaginal RNA which were not detected in plasma. In contrast sequences from the untreated women did not differ between compartments.

Several other studies investigated HIV compartment issues in women. A study from Puerto Rico conducted by Dr Yamamura and colleagues also revealed patterns suggesting that resistance mutations emerged differently in each compartment [21]. Another by Dr Wahl and colleagues revealed discordance between viral load levels in 3 compartments (oral, genital and peripheral blood) from 77 women with detectable viral load (out of a group of 114) [22]

HPV infections and cervical abnormalities

The only report on non-pregnant women that made it, as a slide session was a report concerning the impact of HAART on cervical intraepithelial neoplasia (CIN) presented by Dr Heard [23]. This French prospective study was initiated in 1993, 168 HIV-positive women with CIN were analysed, of the group 80 were defined as having high grade and 88 as low grade CIN. 86 women received PI-containing and 10 NNRTI-containing HAART.

After a median follow up of 17.7 months regression from low grade to normal was observed in 30 women, from high grade to normal in 6, and from high grade to low grade in 31 (n=67, 39.9%). Among women treated with HAART the regression rate was twice as high as it was for women without HAART. It was concluded that 'HAART significantly increased reversion to normality or change to lower grade.' They are currently conducting studies to further evaluate the impact of HAART on HPV infection.

Another report from Dr Luque and colleagues also reported a beneficial effect of antiretrovirals on HPV and that women receiving therapy were less likely to have abnormal Pap smears [24]. These reports describing the protective effect of HAART against pre-cancerous conditions further substantiate data presented last year by Dr Howard Minkoff and colleagues [25]

Finally a report from the WIHS highlighted a concern with regards to the reliability of using different testing methods to predict abnormal cytology [26]. Data were compared from 1370 HIV-positive and 224 HIV negative women who had undergone cervical cytology, colposcopy and biopsy where these were available. Biopsies were performed on 603 (44%) and positive women at least once during 1015 colposcopy visits and 145 (69%) of negative women over 116 visits.

The positive predictive value of abnormal cytology for CIN was 619/854 (72%) for positive women and39/65 (55%) for negative women and the positive predictive value of a positive colposcopy was 512/720 (71%) for positive women and 44/80 (55%) for negative women. The investigators caution that 'The correlation between either cervical cytology or colposcopic impression and biopsy is poor. Liberal use of biopsy is essential for the proper management of women with abnormal smears'. Obviously this message is especially important for HIV-positive women given that it has been demonstrated that immune suppression by HIV speeds up progression of cervical abnormalities [27].

Conclusion

This is probably less of a conclusion and more of a wish list. In the developed world vertical transmission rates are down to virtually zero and we are able to use words like 'elimination' in this context. But in the developing world, women's health is rarely addressed above and beyond their role in transmission of HIV. We support the comment from one report after the Durban conference, which stated that 'Women's advocates repeatedly express concern that women are being viewed as vessels for treatment and transmission, rather than people in need of treatment themselves' [28]. And we would welcome news of plans for studies that also address maternal health.

In addition, although we applaud the work of women's cohorts such as the WIHS, much information about the performance of anti-retroviral in women as compared to men is still unknown, and women still make up only 18% (at the higher end of the range) of subjects enrolled in clinical trials. We have often discussed the reasons for this but would like to make a final plea for better representation in trials of women overall. At a community meeting prior to the Chicago conference Julie Davids from ACT-UP Philadelphia reminded us, that this issue was not just about fairness or feminism or reflecting respective numbers in the epidemic but most importantly clinically 'it's about statistical significance'

A report on paediatric studies from this conference will follow in HTB Volume 2. Issue 3. April 2000.

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Update on HIV Drug Resistance from the 8th Conference on Retroviruses and Opportunistic Infections

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Resistance of HIV-1 to a growing number of drugs is a significant factor that limits the success of antiretroviral therapy. In contrast to previous years, no single slide session was devoted to drug resistance at this year's Conference on Retroviruses and Opportunistic Infections. However, several oral presentations at various sessions as well as a number of posters presented new or updated information on this topic.

The following review summarizes data regarding patterns of resistance to existing drugs, resistance to newer antiretroviral agents, the problem of primary drug resistance (spread of drug resistance through HIV-1 transmission), and drug resistance testing. Because of the large number of posters in this area, only those considered to be the most clinically significant or important will be covered.

Cross-resistance among nucleoside reverse transcriptase inhibitors (NRTIs)

When the NRTI's first entered into clinical practice, resistance was thought to be relatively drug-specific. There were mutations that conferred zidovudine (ZDV; AZT) resistance, those that conferred resistance to didanosine (ddI) and zalcitabine (ddC), the unique pattern of resistance to lamivudine (3TC), and more recently mutations that confer resistance to abacavir (ABC). Resistance to d4T was difficult to pin down, either genotypically or phenotypically. Over the last one or two years, however, a growing appreciation for the extent of cross-resistance among the NRTI's has emerged. In particular, it is now understood that high-level ZDV resistance can confer cross-resistance to most other NRTI's.

Several presentations at this meeting provided additional evidence for cross-resistance between ZDV and d4T. Duan et al [1] studied inhibition of purified RT from a pair of ZDV sensitive and resistant clinical isolates of HIV-1. Enzyme from the ZDV-resistant isolate showed approximately 10-fold resistance to AZT-triphosphate and d4T-triphosphate (the activated forms of AZT and d4T), and also showed modest (3-fold) resistance to 3TC-triphosphate. These findings provide additional evidence for cross-resistance between ZDV and d4T and may provide a biochemical explanation for the lower efficacy of d4T in patients with prior ZDV treatment.

These results are supported by findings from NARVAL, a trial of genotypic and phenotypic resistance testing [2]. The association between presence of 3 or more ZDV resistance mutations with virologic response to d4T, ddI, ABC, or 3TC in the control (no resistance testing) arm was studied. Presence of these 3 or more ZDV resistance mutations at baseline was associated with a worse virologic response at week 12 to regimens that included d4T (P=0.0364) ddI (P=0.0213), and ABC (0.0676). These results confirm the effect of ZDV resistance mutations on response to other NRTI's, even when they are part of a HAART regimen.

Similar results were obtained by Shulman et al [3] in an analysis of ACTG 302. In this study from the pre-HAART era,

ZDV-experienced patients who subsequently received d4T monotherapy were unlikely to show a virologic response (0.3-log10 decrease in HIV-1 RNA from baseline) in the presence of ZDV resistance mutations (215Yor F, or a combination of mutations at codons 67, 70, and 219). Of note, a mutation at codon 70 alone (often the first ZDV resistance mutation to emerge) was associated with a greater likelihood of virologic response.

Different results were observed by Cohen et al in the VIRA3001 study, a randomised trial of phenotyping vs standard of care [4]. In that study, the frequency of ZDV resistance mutations among patients who had received only a single thymidine analogue prior to study entry as 61% for ZDV-treated patients and 69% for d4T-treated patients, respectively. Among the ZDV- or d4T-experienced patients who switched to a d4T- or ZDV-containing regimen, those who switched from ZDV to d4T (n=57) were more likely to have a treatment response at week 16 than were those who switched from d4T to ZDV (n=10) (60% vs 20%; P=0.036) in an intention-to-treat (missing=failure) analysis. These data should be interpreted with caution because of the small number of patients (10) who switched from d4T to ZDV, and should be viewed in the context of other studies presented here and at earlier meetings showing a reduced response to d4T in patients with ZDV-resistant virus.

Resistance to Abacavir [Ziagen]

One problem in the interpretation of phenotypic drug resistance assays is defining the "break point" or cut-off between sensitive and resistant viruses. Up until recently, these definitions were based on assay variation, rather than on clinical data. Clinically relevant cut-offs for abacavir in the PhenoSense assay (ViroLogic) were determined by Lanier et al [5] using data from four clinical trials of abacavir (CAN 2003, 3001, 3002, and 3009). In each case, NRTI-experienced patients with detectable plasma HIV-1 RNA added ABC to a stable background regimen. Using several different statistical approaches, a significantly better response was observed when the patient's virus was <4.5-fold resistant to ABC as compared to wild-type. As a result, a cut-off of 4.5-fold over wild-type has been established for ABC resistance in the PhenoSense assay.

In a related poster, Melby et al presented data on the emergence of NRTI resistance mutations following long-term initial therapy with ZDV/3TC/ABC in CNA3005 (ZDV/3TC/ABC vs ZDV/3TC/IDV) [6]. To date, 43/262 patients (16%) of patients assigned to the triple-NRTI arm have experienced virologic failure (two consecutive plasma HIV-1 RNA levels >400 copies/mL). One or more NRTI resistance mutations were found in 34/40 samples available for genotyping. Thirty-two of these had an M184V mutation at the first genotype following virologic failure; two patients had 1-2 ZDV resistance mutations in addition to the M184V mutation.

These results demonstrate that as with PI-containing regimens, the most common mutation following failure of this ABC-containing triple-therapy regimen was the 184V mutation, which confers resistance to 3TC and low-level resistance to ABC. Patients who remained on the ZDV/3TC/ABC regimen after virologic failure had reasonably stable virus loads over a median follow-up of 80 weeks (median plasma HIV-1 RNA = 3.5 log10 copies/mL), but showed accumulation of additional resistance mutations in their virus samples (Y115F or ZDV resistance mutations). These results reinforce the concept that although virologic failure may initially be accompanied by limited evidence of drug resistance, more extensive resistance patterns emerge with continued administration of a failing regimen.

Nucleotide reverse transcriptase inhibitors

Tenofovir (TDF) is an investigational nucleotide analogue inhibitor of HIV-1 RT that is in phase 3 clinical trials and recently has become available through expanded access. Previous work has shown that most ZDV-resistant isolates remain susceptible to TDF, and that presence of the 3TC-resistance mutation (M184V) increases susceptibility to TDF.

Miller et al presented an analysis of TDF resistance data and clinical response from Gilead Study 902 [7]. In that study, addition of TDF to background failing therapy resulted in an average reduction in plasma HIV-1 RNA over 24 weeks of 0.58 log10 copies/mL; at 48 weeks patients receiving TDF showed a mean virus load reduction of 0.62 log10. In the current study, baseline phenotypic resistance testing of samples from 53 patients showed a mean reduction in TDF susceptibility of 1.9-fold compared to wild-type and 13.8-fold for ZDV (Antivirogram, Virco). Only four patients had >4-fold reduced susceptibility to TDF at baseline.

The HIV-1 RNA response to TDF was significantly associated with susceptibility to TDF (P=0.007) and ZDV (P=0.035), but not other NRTIs. Isolates from 14 patients obtained at week 48 showed >2.5-fold reductions in TDF susceptibility. A K65R mutation (which confers TDF resistance) emerged in 4 patients and was associated with reduced susceptibility to TDF. Although exact cut-offs for clinical response to TDF based on phenotypic testing have not yet been established, data from this study clearly show a relationship between TDF susceptibility and treatment response, and also suggest that ZDV resistance may play a role in determining response to TDF.

DAPD

Daminopurine dioxalane (DAPD) is a prodrug of dioxalane guanosine (DXG), which is currently in phase I/II clinical trials. The drug has in vitro activity against ZDV- and 3TC-resistant isolates of HIV-1, including those that carry the multi-nucleoside resistance mutation at codon 151. Resistance is conferred to DAPD by the K65R mutation and by the insertion mutation at codon 69 that is also associated with multi-nucleoside resistance.

Studies presented by Feng et al [8] with purified RT from wild-type isolates of HIV-1 demonstrated that DXG-TP is a potent inhibitor, and that the enzyme incorporated the natural substrate dGTP 17 times more efficiently than DXG-TP. The overall efficiency of incorporation of DXG-TP was not affected by mutations that confer resistance to ZDV or 3TC. These data provide biochemical support to the rationale for use of DAPD against NRTI-resistance viruses. Preliminary data presented at ICAAC (Eron et al. 40th ICAAC, Toronto, 2000 [Abstract 690]) demonstrated short-term (15-days) activity of DAPD as a single agent when added to the regimen of

patients failing antiretroviral therapy. However, the utility of DAPD in salvage therapy remains to be determined in randomised clinical trials.

Lopinavir [Kaletra]

An important issue in determining strategies for antiretroviral therapy is the pattern of resistance that can be expected upon failure of a particular regimen. Although a considerable amount of data have accumulated regarding resistance to lopinavir (ABT-378) in isolates from patients failing other protease inhibitors, the small number of patients who fail first-line therapy with lopinavir/ritonavir has limited knowledge regarding expected patterns of resistance and cross-resistance in viruses from such patients. Two posters attempted to address this question.

Brun et al analysed cross-resistance to protease inhibitors among 56 viruses that were highly resistant to lopinavir in an attempt to estimate what patterns of protease inhibitor (PI) resistance might be expected from patients failing lopinavir/ritonavir regimens [9]. Five of these isolates came from PI-experienced patients who had viral rebound when receiving salvage therapy with lopinavir/ritonavir. (To date, no lopinavir-resistant viruses have been recovered from more than 470 treatment-naïve patients who have received this combination for more than 48 weeks.) The fold-change in susceptibility to lopinavir was highly correlated with susceptibility to indinavir and ritonavir, but correlated poorly with amprenavir and saquinavir resistance. For example, viruses with a median 44-fold resistance to lopinavir were only 6-fold resistant to amprenavir. Similarly, viruses from PI-experienced patients failing lopinavir-based salvage therapy had 9- to 99-fold resistance to lopinavir but were <8.5-fold resistant to amprenavir; three of these isolates also remained saquinavir susceptible.

These data suggest that patients who experience treatment failure on lopinavir might still have a virologic response if treated subsequently with amprenavir- or saquinavir-based regimens. Clinical data from a single patient with a virus that developed 25-fold resistance to lopinavir but retained wild-type sensitivity to amprenavir, and had a good treatment response to that drug with plasma HIV-1 RNA levels that dropped to <400 copies/mL at week 12. Although these data are encouraging, it is important to note that the patients in this study had all been treated with other protease inhibitors prior to the use of lopinavir. Different patterns of cross-resistance might be observed depending on the specific mutations that emerge during treatment with lopinavir in previously PI-naïve patients.

In a related study, Bernstein et al examined resistance patterns in HIV-1 isolates from treatment-naïve patients failing antiretroviral therapy in the Abbott M98-863 study (lopinavir vs nelfinavir) [10]. Genotypic data are available from 31 patients who failed lopinavir/ritonavir and from 65 patients who failed nelfinavir. Whereas 13/31 (42%) isolates from lopinavir/ritonavir failures showed 3TC resistance, none had accumulated resistance mutations in the protease gene. By contrast, isolates from 21/65 (32%) patients failing nelfinavir had genotypic resistance of nelfinavir resistance, and 86% had resistance to 3TC. These findings are consistent with the prediction that if patients are monitored closely it is unlikely that lopinavir-resistant viruses will be found in patients failing first-line therapy with lopinavir/ritonavir.

Although the data remain somewhat limited, they provide some reassurance regarding the use of lopinavir/ritonavir as an initial protease inhibitor-containing regimen in patients for whom such therapy is appropriate.

Primary Drug Resistance

The transmission of drug-resistant HIV-1 was first documented in 1993. More recently, a several well-documented cases of transmission of multi-drug resistant HIV-1 have been reported. Since then, there has been growing concern about the potential for widespread transmission of drug-resistant virus. Several presentations and posters at the 8th CROI in Chicago documented the prevalence of drug resistance among patients with newly acquired HIV-1 infection from around the world.

Weinstock et al [11] presented data on the prevalence of drug resistance mutations in HIV-1 samples from 437 treatment-naïve patients from 10 U.S. cities collected during 1997-99. Approximately 10% of these patients were recently seroconverters; the remainder had chronic established HIV-1 infection. Overall, 45 (10%) had mutations associated with drug resistance: 8.5% for NRTI's, 2.5% for nNRTI's, and 0.7% for PI's. Only 1% had evidence of multi-drug resistance. The prevalence of resistance mutations was similar in samples from patients with recent or established infection, arguing against a substantial increase over time in this population.

A contrasting view was presented by Little et al [12]. Patients are identified as having acute infection or as recent seroconverters from eight cities in the U.S. and Canada. Drug resistance was determined by the PhenoSense assay (ViroLogic, South San Francisco) and by genotyping (using ABI sequencing). Samples were characterized as having >2.5-fold or >10-fold resistance to drugs in each class of antiretroviral agent.

A total of 408 patients have been identified by this group. The prevalence of high-level (>10-fold) resistance to nNRTI's and PI's in samples from newly infected individuals increased sharply during 1999-2000 compared to 1996-98. The proportion of isolates with high-level resistance to the nNRTI's increased from 1% to 7% (P=0.001) and for PI's from 2% to 6% (P=0.05). Eight percent of newly infected patients identified after 1998 carried viruses that showed >10-fold resistance to at least one drug, and 4% had resistance to two or more drugs.

The time to virologic suppression (plasma HIV-1 RNA <500 copies/mL) was significantly longer for newly infected patients with viruses that had >10-fold resistance to one or more drugs as compared to those that had sensitive viruses (P=0.05). Among patients who achieved complete viral suppression on an initial regimen instituted during primary HIV infection, there was also a trend toward earlier failure of viral suppression for those with viruses that had >2.5-fold reduction in susceptibility to one or more drugs.

An increasing prevalence of transmitted drug-resistant virus was also noted by Simon et al [13], who reported on 61 newly infected patients identified during 1999-2000 in New York City and Montreal. Overall prevalence of primary drug resistance mutations in samples from this cohort was 26%,

which represents an increase from 16% for the years 1995-98. These numbers may not be representative of the country as a whole, however, given the relatively small numbers and highly selected patient population. Nevertheless, these data show that rates of transmission of resistant virus can vary considerably depending on the group and geographic area under study.

A question that is often asked is how stable drug-resistant variants are after transmission, in the absence of antiretroviral therapy in the newly infected patient. Two abstracts addressed this issue. Garcia-Lerma et al from the CDC [14] identified 10 newly infected patients with unusual mutations at codon 215. A change from threonine (T) to tyrosine (Y) or phenylalanine (F) at this position is associated with ZDV resistance. This resistance mutation requires a change at two nucleotides within the 215 codon (eg, ACC to TAC). Novel variants reported in this poster included 215D, 215C, 215S, and 215E, which are thought to represent intermediates of a 215Y revertant (ie, only one of the two nucleotides at codon reverted back to wild-type).

Fitness assays showed that these partial revertants were more fit than the ZDV-resistant 215Y variant. Although these novel mutations do not by themselves confer resistance to ZDV, they should be considered as markers of previous selection by ZDV, and set the stage for more rapid emergence of ZDV resistance if treatment with ZDV is initiated in patients carrying such viruses.

Daar et al [15] reported on the case of a patient who presented with acute HIV-1 infection and was found to have a multidrug-resistant virus that carried both PR and RT resistance mutations, including the insertion mutation at RT codon 69. Virus load, which initially was 5.48 log10 copies/mL, fell to approximately 3.0 log (1,000 copies/mL) in the absence of treatment. More susceptible virus evolved over a 4-5 month period. At 5 months, a 10-fold increase in virus load above the previous set point of 1000 copies/mL corresponded to emergence of a virus that carried no primary drug resistance mutations.

These data demonstrate that although highly resistant viruses can be transmitted, their reduced replicative capacity may be associated with relatively low virus loads following primary infection. However, emergence of wild-type virus in the absence of drug treatment may subsequently be accompanied by a rise in virus load, most likely as a consequence of superior fitness of the wild-type virus.

Two other reports tracked the spread of drug-resistant HIV-1 in Europe. Yerly et al [16] reported on rates of drug resistance among patients with primary HIV infection in Switzerland. In that country, transmission of drug-resistant virus appears to have decreased over the last three years (1998-2000) as compared to the period 1996-97. The investigators attributed this reduction to the high rates of viral suppression achieved by the widespread availability and use of potent antiretroviral therapy.

Whereas only 10% of patients followed in the Swiss HIV Cohort study had undetectable levels plasma HIV-1 RNA in 1996, that figure increased to 53% in 1999. Yerly et al also noticed significant clustering of cases of primary HIV infection, which is a worrisome finding. Through nucleic acid sequence analysis, they were able to show epidemiologic links among several cases of primary HIV infection. In many instances, transmission occurred even before the index case developed symptoms. This situation is analogous to the spread of other viral infections (e.g., hepatitis A), in which the patient is most infectious prior to development of recognizable symptoms that lead to diagnosis. Efforts at contact tracing and counselling to halt the spread of HIV will be made more difficult if a substantial number of individuals spread the virus during this early "window" period.

Chaix et al reported the prevalence of drug-resistant HIV-1 in France [17]. 108 patients diagnosed with primary HIV-1 infection during 1999 were identified from three cohort studies. The frequency of drug resistance (identified by genotyping) was 6.5% having resistance to NRTI's, 3.7% to the nNRTI's, and 2.8% for the PI's. Samples from two patients showed evidence of multi-drug resistance. Taken together, these results provide strong support for the need to perform drug resistance testing in patients with primary HIV-1 infection prior to initiating antiretroviral therapy.

Resistance Testing and Effect of Drug Resistance on Response to Treatment

Resistance testing is rapidly becoming an essential laboratory tool for help in selecting optimal antiretroviral regimens in HIV-1 infected patients. Several posters at the 8th CROI addressed important issues related to resistance testing and the ability of resistance testing to predict treatment success or failure. A critical question with regard to phenotypic resistance assays is the way in which "sensitive" and "resistant" viruses are defined. Ideally, such definitions would depend on showing that a given drug lost the ability to suppress virus replication at a particular IC50 or fold-resistance. Such data are available for only a handful of drugs, however (see discussion of cut-offs for abacavir, above). In the absence of such data, resistance has usually been defined by default as any level of susceptibility that exceeds the interassay variation (eg, 2.5- or 4-fold). This definition ignores the natural variation in susceptibility of wild-type viruses, however.

To address this shortcoming, Harrigan et al [18] analysed susceptibility data from 1000 isolates obtained from treatment-naïve patients around the world using the Antivirogram assay (Virco). They found that 97.5% of isolates had shifts of less than 2.5- to 4-fold for the PI's, less than 3.5-4.5-fold for the NRTI's, but up to 5-10-fold for the nNRTI's. Based on these data, new cut-offs have been defined for the Antivirogram assay.

Virtual Phenotype

Interpretation of genotypic data is often difficult and confusing for patients and clinicians who are not experts in HIV-1 drug resistance. One approach to interpreting the genotype is the so-called "Virtual Phenotype". The Virtual Phenotype uses computer-based artificial intelligence software to predict the likely phenotype for a given genotype by "matching" the genotype of a patient's virus to other viruses in a database of >18,000 samples with paired genotypes and phenotypes. The phenotype of all the matching viruses is averaged, and reported as the Virtual Phenotype.

Previous work has shown that in most cases the virtual

(predicted) phenotype is reasonably well correlated with the actual (measured) phenotype of a given virus. To validate the Virtual Phenotype against clinical response data, Graham et al [19] analysed baseline samples from 191 patients enrolled in VIRA 3001, a randomised trial of phenotyping vs standard of care. The Virtual Phenotype was a significant independent predictor of treatment outcome in several statistical models, and in some cases appeared to be more predictive than genotype.

These results provide additional support to the validity of the Virtual Phenotype as a tool for interpreting viral genotypes. However, the reliability of the Virtual Phenotype depends on a number of factors, including the specific mutations that are put into the search for a match, the number of matches found, and the distribution of drug susceptibility among the matches. Further work is needed to validate the Virtual Phenotype against other forms of resistance testing in clinical trials.

"Inhibitory Quotient"

Another potential tool for the interpretation of resistance data is the "Inhibitory Quotient". The IQ attempts to relate the measured trough level of a drug to the IC50 of the patient's isolate for that drug (corrected for binding to plasma proteins). A high IQ means that the trough plasma concentration significantly exceeds the amount of drug needed to inhibit the virus in question; a low IQ suggests inadequate drug levels or a highly resistant virus.

Kempf et al [20] estimated IQ's for patients receiving RTV-boosted IDV therapy for treatment of IDV-resistant virus. Phenotypes were predicted from genotypic data using the Virtual Phenotype. Response rates were significantly greater in patients with HIV-1 that was <6-fold resistant to IDV by Virtual Phenotype as compared to patients with virus that was >6-fold resistant to IDV ($P<0.05$). Using the Virtual Phenotype and measured trough concentrations of IDV to calculate a "virtual" IQ, the investigators found that response rates were significantly higher among patients with an IQ>2 as compared to those with an IQ<2 ($P<0.003$). These results suggest that combining phenotypic data with drug levels might be particularly useful in predicting treatment response. However, adjusting drug doses on the basis of the IQ in an attempt to overcome drug resistance may not be advisable, since the safety of very high drug levels that might be required in certain cases has not been evaluated.

Genotypic Resistance

Updates on two recently completed studies of genotypic resistance testing were presented at the meeting. Tural et al presented follow-up data on the Havana study, which compared the utility of genotypic resistance testing, expert advice, or both as compared to standard of care in selecting salvage regimens for patients experiencing failure of antiretroviral therapy.

Genotyping and expert advice each resulted in significantly better virologic response. Response rates (% of patients with virus load <400 copies/mL at week 24) were 57.5% for the genotype arm vs 42.4% for the control arm ($P=0.01$), and 59.1% for the expert advice arm vs 41.1% for the no-advice arm ($P=0.003$). The best response rates were observed in patients who received both genotyping and expert advice as compared to patients who received neither genotyping nor expert advice (69.2% vs 36.4%, respectively; $P=0.001$). These results suggest that although expert advice is helpful, the availability of genotypic resistance assays leads to further improvements in virologic outcome of salvage therapy. In contrast to some other studies, the Havana study found that genotyping made the biggest difference in patients who had failed 3 or more regimens.

De Luca et al [21] presented final results of the Argenta study, which had been presented in part at the Durban meeting. In this study, 174 patients were randomised to genotype or standard of care. Twenty-five percent had failed >3 HAART regimens and 41% were triple-class experienced. Although a significant difference in the percent of patients with virus loads <500 copies/mL was observed at 12 weeks favouring the genotyping arm (27% vs 12%, $P=0.02$ for genotype and standard of care, respectively) the difference between arms was not statistically significant at week 24 (21% vs 17%, respectively).

Failure to observe a larger difference between the groups may be a result of the imbalance between arms with regard to a number of important parameters at study entry, including a larger proportion of patients with >2 primary resistance mutations and greater proportion of nNRTI-experienced patients in the genotyping arm. By contrast, duration of prior nNRTI therapy was longer in the standard of care arm. A beneficial effect of genotyping was more easily demonstrated when the analysis focused on adherent patients failing their third or earlier HAART regimen. These results are consistent with those of Viradapt and the NARVAL study, which suggest that treatment adherence and number of prior treatment regimens play an important role in determining the usefulness of drug resistance testing.

Two presentations on resistance testing reported the seemingly paradoxical observation that in some cases presence of resistance mutations appeared associated with an increased chance of treatment success. Genotypic analysis of isolates from patients participating in the NOVAVIR study (ANRS 073) provides additional evidence of cross-resistance between ZDV and d4T [22]. In that study, ZDV-, ddI-, or ddC-experienced patients who were 3TC- and PI-naive were randomised to ZDV/3TC/IDV or d4T/3TC/IDV. Similar virologic responses were observed in the two arms. A majority of patients had evidence of one or more ZDV resistance mutations at entry.

Curiously, presence of ZDV resistance mutations was associated with a significantly lower risk of virologic failure in both the ZDV- and d4T-containing arms. Similar results were reported by Tasker et al [23] who found greater decreases in plasma HIV-1 RNA and greater increases in CD4 cell count at six months among patients carrying drug-resistant virus. These results suggest the possibility that patients with wild-type virus were poorly adherent to therapy while on NRTI therapy, hence the absence of resistance mutations at baseline.

Summary

What were the most important take-home messages of the conference with regard to drug resistance? First, that cross-resistance between the NRTIs is more widespread than

previously recognized, but that newer drugs in this class (as well as the nucleotide RT inhibitors) may have an important role in salvage therapy. Second, although transmission of drug resistant virus remains low in some cities, rates of primary resistance to the newer drugs (nNRTI's and PI's) increased sharply over the last two years in other cities, and might be associated with reduced effectiveness of treatment.

These data provide a rationale for performing drug resistance testing prior to initiating therapy in settings with high prevalence of drug resistant virus among newly infected individuals. Third, more data are needed in order to better define the cut-offs for sensitive and resistant virus in phenotypic assays, but improvements are being made. Fourth, the Virtual Phenotype appears to be a useful tool for interpreting genotypic data, although prospective clinical validation is needed. Finally, resistance testing appears to be useful in selecting salvage regimens in most studies, but further refinements are needed.

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Update and review of bone studies

Simon Collins for HIV i-Base

Previous reports of risk factors associated with associated changes in bone mineral density (BMD) in reports from the lipodystrophy and Glasgow meetings in October and November issues of HTB have highlighted the likely contribution of HIV and possibly HAART. Further evidence of seriousness of these complications was indicated in an excellent overview of bone mineral changes and lactic acidemia in a lecture by Andrew Carr [1] and by the 16 or so studies presented as posters. These new studies looked to broadly determine the role of HIV, HAART or individual drugs, the causative mechanisms and whether a link is established with symptoms of lipodystrophy. Two late-breaker abstracts presented sobering data on the risk of BMD changes in children.

Prevalence studies

The four studies looking at prevalence all found evidence of reduced BMD, generally detected by DEXA scan and evaluation by z-score and t-score, in HIV-positive patients, often without finding a link to HAART or individual drug exposure. Unless stated otherwise, osteopenia follows the WHO definition of t-score $^{-}1.0$ - $^{-}2.5$ and osteoporosis as t-score < $^{-}2.5$. One of the most interesting of these was from Knobel and colleagues from Barcelona. [2]

This group compared lumber spine and femoral neck BMD t-scores and z-scores in three groups of HIV-positive patients (treatment naïve, PI-experienced and non-PI experienced) and HIV-negative controls. Osteopenia was found in 4/16 (25%) of naïves, in 12/30 (40%) of PI-treated patients, in 3/

12 (33 %) of non-PI-treated patients and in 8/50 (16%) of HIV-negative adults. Difference reaches statistical significance only between HIV-infected patients (34.5%) versus seronegative controls (p=0.00001 OR: 6.2 CI 95%: 3.1 – 12.6). Osteoporosis was present in 21% HIV patients compared to 5% of HIV-negative controls (p=0.0009, OR: 5.1 CI 95%: 1.7-18.5). The only difference relating to the potential role of individual treatment was that the 17 patients exposed to indinavir had lower z-score in femoral neck compared to HIV-infected patients not exposed to indinavir (-1.4 vs).7, p=0.02).

Lawal and colleagues from St Roosevelts Hospital in New York compared results between from DEXA scans in pre-HAART and post-HAART studies and found that baseline total bone mineral content, calcium and density were similar in both groups. [3] Incidentally, neither of these studies (using oxandrolone or rHGH for wasting) showed any improvement on BMD over the course of the study. [4, 5]

Link to lipodystrophy and metabolic changes

Four posters investigated links with lipodystrophy or metabolic changes. Andrew Carr's group in Sydney assessed possible relationships between osteopenia and demographics (age, smoking, exercise), symptoms (lactic acidemia, weight loss, neuropathy), body composition, metabolic (lipid and glycaemic parameters, lactate/anion gap) and HIV disease (ARV therapy and duration, AIDS diagnosis, CD4 count, viral load). [6]

Of 221 HIV-positive otherwise healthy male patients, enrolled in a lipodystrophy prevalence study, 32 were drug naïve, 42 were receiving NRTIs and 147 were receiving PI and NRTI treatment. Osteoporosis and osteopenia were found in 7 (3%) and 44 (22%) respectively. Changes in BMD were also found to be statistically significantly related in a multivariate analysis to higher lactate levels (OR 2.39 [95% CI 1.39 to 4.11] per 1 mmol/l increase; p = 0.002) and lower weight pre-ARV therapy (OR 1.06 [95% CI 1.02 to 1.11] per 1 kg decrease; p = 0.006).

The link between osteoporosis and increased lactate levels was not confirmed by Claxton and colleagues, perhaps because of the smaller study size (n=30), although osteopenia (WHO definition) and increased lactate levels (>2.5mM) were present in 43% and 30% respectively in this group. [7]

Effect of Indinavir and Ritonavir on formation and reabsorbion

Although presentations at the conference sometimes provided a contradictory link to HAART and individual treatments, Wang and colleagues form Washington University Medical School provided evidence of different effects on bone regulation from each of these PIs.

Indinavir produced a dose dependent decrease in alkaline phosphatase when added to murine osteoblast cell lines, an effect that was repeated in an ex-vivo calvarian culture system. When injected intraperitoneally in mice for two weeks the researchers reported a tenfold decrease in osteoblast colony forming units. In vitro culturing showed an inhibitory effect of indinavir, but not ritonavir, on both adipocyte and osteoblast differentiation.

Opposite inhibitory effects were observed when the drugs were tested with osteoclasts. Ritonavir added to mature osteoclasts on bone slices, prevented resorbtion, even though OC number remained unchanged. Ritonavir was also found to block osteoclastogenesis when administered to mice. Neither effect was observed with indinavir. [8]

Avascular Necrosis (AVN)

A comprehensive review of the medical records of 2493 patients from the Johns Hopkins HIV Clinic found 17 reports of AVN of the hip between 1995-2000 over 6900 person-years. Eleven cases were bilateral and 6 were unilateral. This produced an incidence rate of 2.47 per 1000 person years (population-based incidence is for AVN is 0.04). Keruly and colleagues found a significant annual trend (p=0.05) over this period. They found no association with age, concurrent lipodystrophy, PI or NNRTI use or specific RTI-use compared to the rest of the cohort. The strongest association in this study linked to low CD4 count and duration of infection. [9]

Bone changes in children

Several studies at the conference reported bone mineral changes as a common occurrence in children, both as separate reports and within the context of increased reporting of lipodystrophy symptoms.

Dr Stephen Arpadi reported significant reductions in total body bone mineral content (TBBMC) in a group of 51 perinatally infected children (age 4.2-14.7 yr) when compared to 282 HIV negative children of a similar age and racial background. These reductions progressed with age (HIV/age interaction, p=0.032) and the negative effect of HIV status on TBBMC (p<0.0001) persisted after adjustment for body size, race, gender and bone area. No association was found between TBBMC and PI-use, CD4 count or CD4 percentage. [10]

Data from the Italian group lead by Dr Alessandra Viganò (who incidentally reported optimal viral suppression <50 copies/ml in 33/35 of their HAART-treated children) compared lumbar spine and total body BMD in 35 HAART treated, 5 treatment naïve and 314 HIV-negative controls (age range = 4.5-18.5 yrs). Differences were found to be significant between HAART-treated and control children (p=0.004 and p=0.0001 respectively, compared to controls). Looking at markers of bone formation (bone alkaline phosphatase and serum N-terminal propeptide) and resorption (urinary N-terminal telopeptide) Viganò identified an increased rate of bone turnover as the pathogenic mechanism for bone mineral loss in these children. [11]

Five cases of AVN were reported among 1011 perinatally infected children enrolled in PACTG Study 219, two at study entry and three during follow-up. This represents an incidence rate of 94 per 100,000 person years. [12]

Conclusion

Most studies at the meeting concluded that it was too early to recommend routine BMD monitoring as part of routine management as osteopenia is an asymptomatic condition, although it is difficult to understand how changes in BMD can be followed without baseline and subsequent monitoring. Suggestions for management included promoting adequate calcium intake and weight-bearing exercise together with an

assessment of other risk factors (smoking, exercise, malnutrition and hypogonadism).[2] Deferring treatment, which was also recommended, while avoiding complications over the short-term, is not going to impact on the reality of lifelong treatment and is an option that isn't available to children and adults who are already dependent on treatment.

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C O M M E N T

Complications from osteopenia are increasing, and as Andrew Carr pointed out 'physician denial promotes patients non-adherence'. It is still unclear, however, as with lipodystrophy, what the relative contributions of HIV-infection itself and any treatments might be in the development of these problems.

In this light, clinicians may be encouraged to review policy on a regular basis toward a more proactive management. Regardless of the nature of osteopenia DEXA should be considered for any patient with a history of HIV-infection of several years.

Given the availability, relatively low cost and non-invasive nature of DEXA scans, and the broad bone and fat distribution changes being reported, the information they will provide in the future could become invaluable information for assessing risk and rate of progression and response to intervention strategies.

Management strategies including calcium and vitamin D supplementation as well as encouraging regular weight-bearing exercise are warranted until adequate treatment is defined.

Treatment Interruptions, structured and unplanned…Immunotherapy and what's in store

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So here goes the pendulum again, this time against drug [read antiretroviral combination] treatment. Several studies were presented at this conference that argued for later time of starting treatment with HAART as no clear clinical advantage could be determined in those who started treatment with T4 cell count levels above 200 cells/mm^3. This was also since the balance between benefit (avoidance of HIV-related opportunistic infections and tumours) and drug associated toxicity appears to be swinging to the latter. Lipodystrophy, increased cardiac risk, facial wasting, have all become common words linking together a general physical, symptomatic and psychosocial constellation of problems at least in some part due to treatment (iatrogenic).

I suppose the most important issue to come out of the conference on treatment interruptions is that they are not all alike. The information on structured (i.e. planned and repetitive) interruptions is much stronger for primary or early infection than for chronic or late-stage disease. This is logical in the regard that HIV specific T4 helper responses are still relatively preserved and thus the host immune function retains more ability to suppress HIV. Bruce Walker summed up the oral session on this subject with a presentation on the ongoing work he and Eric Rosenberg have presented before. Fourteen subject at primary HIV infection [PHI} with a very high median viral load of 10million copies/mL had treatment interrupted when they achieved <50 copies/mL and then restarted if the HIVRNA rises above 5,000 copies/mL.

To date 6 subjects have not failed by these criteria whereas 8 subjects restarted and re-suppressed and after a second interruption only one subject failed to stay low initially. At a later time-point several have either started treatment or rebounded. These data are very preliminary and of course only apply to the very difficult to identify group of PHI patients. However it is tantalising to believe that this would suggest that in some initially infected subjects control of HIV is achievable by a combination of treatment for a period of time followed by exposure to HIV again. Several studies are examining the utility of using HIV vaccines to expose PHI HAART treated patients to HIV genetic material without using HIV itself.

Marty Markowitz, from David Ho's group, presented data on other PHI treated subjects who then had STI's [1]. These subjects were seen a little later in the course of their infection (median 65 days after infection) than those presented by

Walker. What became clear is that the responses were also less impressive with only 3 subjects out of 5 studied controlling HIV after STI, 5 had levels between 5000 and 20,000 copies/mL and 7 restarted treatment. So it would appear that even a short delay in treatment might have negative implications for the outcome of this strategy.

When it comes to those who have had longer periods of treatment with HAART and in who therapy was started well after seroconversion the results of STI studies are less than earth shattering. The largest study to report to date and what looks like the one which will define the lack of benefit of this approach is the Swiss-Spanish Intermittent Treatment Trial [2]. Each new conference brings less hopeful noises form this group and it seems that when it finally gets to peer review the outcome is likely to show an heterogeneous response to STI in this population. Currently there are 132 subjects entered (less than 50 copies/mL for over 6 months) of that 99 have been followed through 52 weeks. Subjects had 4 cycles of 2 weeks off 8 weeks on therapy and then stop until HIV RNA rose to 5,000 copies/mL. Currently 21% have achieved the aim of not having to restart at this time-point. Although not data yet is available concerning the HIV specific cellular immune responses at last eye-balling the data this does not seem to be a fantastic strategy.

For those subjects however who are losing control of their virus and whom are at later stage of disease there may be more logic to stopping therapy for a while. The balance lies between allowing the viral swarm to settle down to a more sensitive mix of strains for the next therapeutic opportunities arise. Steve Deeks presented more data from his cohort of failing subjects in whom he has well characterised resistance patterns and also fitness of virus swarm after ceasing therapy [3]. He showed that in 19 subjects with detectable virus undergoing an STI of median duration of 18 weeks that the median T4 drop was 95 cells/mm^3 and a viral load increase of 0.74 log10copies/mL. 18 subjects showed a reversion to wild type of protease inhibitor sensitivity. During follow-up on salvage regimen 47% achieved a viral load <50 copies/mL and failure to suppress resulted from persistence of resistance and re-emergence of virus related to prior therapy

So what did the 8th Conference on Retroviruses and Opportunistic Infections have on offer as immunotherapy.

Well there was a little further information on therapeutic vaccines [4]. Jin and colleagues from Rockefeller University in New York enrolled 4 subjects to receive HAART after PHI as well as four vaccinations with a combination of two vaccines HIV-gp160 and the canary pox vector vCP452 expressing HIV gag ,pol env and nef , the new vaccine form Aventis-Pasteur. No adverse events occurred and the vaccinees developed increased antibody responses to envelope proteins and to p24 antigen. In addition 6/14 mounted a temporary HIV specific T-helper response. A disappointing response perhaps but maybe an indication that with better antigens and improved adjuvants then this approach may yield some benefits.

Hecht and co-workers from the University of San Francisco presented some information on the utility of combining interleukin-2 (IL-2) with HAART in PHI [5]. Subjects received Combivir and nelfinavir, with or without up to 6 cycles of IL-2 7.5MIU twice daily for 5 days. To date 28 subjects (3 IL-2) have been followed for greater than 24 weeks. Apart from a weak trend to better viral suppression in the IL-2 treated group there did not appear to be benefits from this intervention in the short-term.

IL-2, however did seem to be beneficial for those subjects who received it in ACTG328 presented by Ron Mitsuyasu [6]. In this large multi-centre US study in subjects starting HAART with T4 counts between 50 and 350. At week 12 if less than 5000 copies/mL subjects were randomised to HAART alone (N=52) or HAART plus continuous IL-2 (CIV) 9MIU OD for 5 days every 8 weeks (N=54) or HAART plus subcutaneous IL-2 (SC) 7.5MIU BD for the same cycle duration and frequency. After 6 cycles and an improvement in T4 count >100 and >25% subjects could switch to SC form CIV IL-2. Results are shown in the table below.

Median CD4	HAART	HAART plus CIV IL-2	HAART plus SC IL-2
week 12	283	247	247
week 60	376	675	579
week 84	396	800	614
week 84-12	121	480	302
% with >50% rise week 12-84	41	86*	77*

**p<0.001 vs HAART alone*

Clearly there is a significant T4 advantage to this intervention and the ESPRIT and SILCAAT studies are now ongoing in order to determine if these T4 cells protect as effectively as those produced by HAART. Interestingly the rise in the SC group over 60 weeks was similar to that seen in the UK IL-2 Vanguard study which did not require the subjects to take antiretroviral agents. [7] Currently the TILT study is recruiting at the Royal Free, UCH and Brighton Hospitals to ascertain if patients could switch from Antiretrovirals to Interleukin-2 as an alternative treatment. .

Further supportive evidence for the role of IL-2 in HIV management came from a long term follow-up analysis of subjects from the US National Institutes of Health who have received IL-2 for greater than 3 years [8]. In this group what is clear is that of the 746 cycles of IL-2 administered to 77 subjects the ratio of cycles/subject decrease from 3.5:1 at 6 months to 0.1:1 at 84 months. Mean interval at that time was 26 (range 2-60 months). This suggests that at least in those who receive antiretrovirals in conjunction with IL2 the cycle rate can be sustained at a low level. Functional immunity also seems to improve over time in subjects on IL-2. Durier and colleagues examined 65 subjects from the French ANRS protocol where they received stavudine (d4T) plus lamivudine (3TC) plus indinavir with or without cycles of IL-2 at 7.5MIU BD for 5 days [9]. After Week 56 median increase in T4 cells was 886 (118-2,487) in the IL-2 group compared to 232 (-30-1,204) in the control group. Increases in CD45RACD62L (naïve T4 cells) was greater in the IL-2 group (475 compared to 83; p<0.001). The proliferative responses to candida and tetanus improved to a greater degree in the IL-2 treated patients (p<0.001).

All these data point to interleukin-2 being the most likely first

licensed candidate for HIV immunotherapy. There are many trials ongoing and the toxicity profile although unpleasant during a cycle is neither dangerous nor prolonged. In addition these and other studies appear to show if anything that the treatment becomes more rather than less effective over time. Other cytokines such as IL-12 may be beneficial in HIV disease and are also currently under study.

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Primary Infection and Treatment Issues

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Over the last six months the belief held by researchers looking at treatment in early infection was vindicated by the results from Bruce Walkers group at Massachusetts General Hospital. This showed the possibility that early treatment can generate a sufficient immune response to make intermittent (and possibly no treatment at all) an achievable goal. [1] Indeed, even the newly revised more conservative US treatment guidelines retain the recommendation to start treatment if early infection is detected. The theoretical rationale for early intervention being stated as:

- to suppress the initial burst of viral replication and decrease the magnitude of virus dissemination throughout the body;
- to decrease the severity of acute disease;
- to potentially alter the initial viral "set point," which may ultimately affect the rate of disease progression;
- to possibly reduce the rate of viral mutation due to the suppression of viral replication;
- to possibly reduce the risk of viral transmission;
- to preserve immune function.

Such considerations considerably strengthen the importance of early diagnosis and a greater awareness of signs of seroconversion both in GUM/STI and primary care clinics. Over 30 presentations reported on treatment, diagnostics, infectivity, resistance and immunological responses during primary infection.

Diagnostics

Primary HIV Infection (PHI) is defined as the period following infection but before seroconversion. This usually takes 2-4 weeks, but can take several months and has been documented in one case to take 10 months. During this asymtomatic period routine HIV tests (ELISA and Western Blot) will generate a negative result although HIV RNA levels are very high (often in the millions/mL), therefore either viral load or p-24 antigen tests can be used to confirm a suspected case of PHI. A combined HIV antibody and p-24 assay developed by Bio Merieux and a combined HIV antibody and antigen assay from Abbott were presented in posters, both with the promise of shortening the period post infection before detection [2, 3].

The practical application for these assays may be more for public health blood screening programmes than individual cases, where a routine viral load assay would generate a positive result in a shorter period. Indeed, Fiebig and colleagues using modelling based on the slope of viral load increase and viral doubling time estimated that a regular RNA viral load test sensitive to 50 copies/ml would already detect primary HIV infection 7 days prior to a p-24 antigen test and 12 days prior to an anti-HIV antibody test. [4]

Infectivity, transmission and seroconversion symptoms

High levels of viral load in the weeks post infection and the effect of coinfection with other sexually transmitted infections presents a greater risk of infectivity than during chronic infection. Five cases of secondary transmission, prior to symptoms of seroconversion, were reported by Picher and colleagues (one M-M, three M-F and one F-M). The transmission pairs were identified from US and European cohorts and confirmed by phylogenetic analysis of pol sequences.

Transmission to the infected partner occurred a median of two days prior to seroconversion symptoms occurring in the index case (range –7 to +7 days). Median peak viral load in the index cases was 6 million copies/ml (range 5.3-7.2 log), other STIs were confirmed in two cases and semen RNA exceeded blood plasma levels in the one case it was measured. A second study from this group looked in further detail at the association between viral load levels in blood and semen during PHI. [5]

Speed of onset and severity of seroconversion symptoms were both found to be highly predictive of risk of progression to CD4 <200 cells/mm3 (for fever, fatigue and myalgia – but not rash, headache or arthralgia).[6]

Adjusted hazard ratios (CI95%) for progression and incubation and duration cut-offs in this study were as follows:

Features	ARH (CI95% of progression to AIDS/CD4<200
Fever	Inc <2.5d: ARH 5.8 (1.7-19.1), p=0.004 Duration >11d: ARH 8.1 (2.4-27.7), p=0.0009
Fatigue	Inc <21d: ARH 2.7 (0.9-8.3), p=0.06 Duration >17.5d: ARH 3.1 (1.1-8.9), p=0.03
Rash	Inc <22d: ARH 1.4 (0.4-4.6), p=0.06 Duration >10d: ARH 1.7 (0.5-5.4), p=0.3
Headache	Inc <23.5d: ARH 1.8 (0.6-5.5), p=0.3 Duration >13d: ARH 4.1 (1.1-14.2), p=0.02
Myalgia	Inc <25.5d: ARH 3.8 (1.0-14.4), p=0.04 Duration >11d: ARH 8.0 ((1.6-38.3), p=0.009
Arthralgia	Inc <19d: ARH 2.8 (0.6-13.6), p=0.2 Duration >15d: ARH 8.5 (0.8-92.2), p=0.07

Transmission of drug-resistant HIV

Transmission of virus resistant to each and all classes of currently available drugs has already been reported for all methods of transmission (sexual, needle sharing, needlestick,, perinatal). The extent of such transmission are still reported to vary by geographical area.

16/61 newly-infected individuals (1999-2000) from New York (n=55) and Montreal (n=6) treated at the Aaron Diamond Institute showed a prevalence of 26% resistance conferring amino acid substitutions, including 5 cases of multiple class MDR. Phenotypic resistance (from 58 tests using PhenoSense assay) showed an overall prevalence of reduced susceptibility to any drug of 38% (>2.5 to 5-fold: 28%; >10-fold: 7%). Lack of phenotypic susceptibility in these samples was roughly evenly split between NNRTI and PI. Hypersensitivity, (<0.4-fold) to any NNRTI was seen in 10 cases (17%) and to any PI in 4 cases. This represented a statistically significant increase in transmission of drug resistant virus compared to levels of 16% previous years (1995-98), p<0.05. [7]

A larger US study, looking at phenotype resistance and subsequent response to treatment in over 400 treatment naïve subjects with recent infection, found 8% to with >10-fold susceptibility to at least one agent and 4% showing >10-fold reduced susceptibility to at least two classes. Although the importance of referencing separate sensitivity scales for different drugs in now recognised the time to achieve undetectable viral load (<400 copies/ml) was significantly increased in patients with >5- and 10-fold reduced susceptibility to one or more ARV at baseline (p=0.005 an p=0.04). [8]

Closer to home, genotypic mutations to at least one class of ARV was detected in 10% in three French cohorts (n=108) – 6.5% NRTIs, 3.7% to NNRTIs and 2.8% to PIs. [9]

A single case study was also shown of a 32-year old man with seroconversion symptoms whose phenotype profile showed >2.5-fold resistance to all RTIS (except ddI and ddC), all NNRTIs and al PIs (except saquinavir). Electing not to take treatment, viral load and CD4 count were monitored and remained constant over the next 4 months (2.9-3.1 log10 copies and 504-629 cell/mm3 respectively). At month 5, co-incident with a log-fold increase in HIV RNA viral genotype showed a reversion to viral type. Although most people expect the resistant strain to remain archived, and likely to return should ARV treatment be initiated in the future the implication of reduced fitness from resistant virus deserves further study. [10]

Treatment in Primary Infection

One of the most important reports concerning treatment in was presented in a State of the Art lecture on supervised treatment interruption. [11] Bruce Walker updated results from his cohort of 14 patients that have been treated prior to seroconversion. All patients had been maximally suppressed with antiretroviral regimens for at least eight months prior to the first treatment interruption (mean = 547 days, range 270-1081 days). Mean viral load at diagnosis was 10 million copies/ml.

The study design included restarting treatment if viral load rebounded to >50,000 copies/ml at any time or if it remained >5000 copies/ml for >3 consecutive weeks. Primary endpoints included control of viraemia without therapy, boosting of virus specific immune responses following a regulated exposure to autologous virus and control of viraemia after subsequent interruptions.

Seven patients have so far discontinued treatment once and maintained viral suppression, one of whom has restarted by choice, despite not reaching protocol defined endpoints. This person subsequently stopped treatment for a second time and controlled viral load for almost 300 days before deciding to restart again at a viral load level of only 600 copies/ml. The remaining six of these seven patients all saw their viral load rebound , but not above protocol defined endpoints before they all drove viral levels back down and maintained relative viral control at <5000 copies/ml for between 80-450 days.

The remaining seven patients rebounded above protocol limits following their first interruption and needed to restart therapy after 5-60 days off-treatment (five of whom rebounded to >50,000 copies/ml). All but one of these patients have subsequently controlled viraemia. Time to breakthrough following a second treatment interruption extended considerably in these patients. Mean time to restart was 36 days following the first interruption and 184 days following the second. A highly statistically significant increase in magnitude and breadth of CTL responses was also reported following this second interruption. Only one patient failed to control viraemia (after 4 treatment interruptions) and remains at 7445 copies/ml after 128 days off therapy – and appears likely to restart.

It was clearly acknowledged that this is a small cohort, treated very early after infection, and that neither long term durability nor clinical benefit have been proven. Nevertheless the importance of this study within a PHI as well as STI report is that it demonstrates extremely optimistic results supporting immunological control similar to that seen in long-term slow progressors.

A further ten other posters provided cautions and practical information for treatment in primary infection. Success shown in the Walker study may be the only justification from starting treatment many years before CD4 levels are reached for initiating treatment in chronic infection.

Time to initiation of HAART post infection correlated directly to chance of success in a study from Geise and colleagues

from Washington. [12] All 37 patients starting within 120 days or seroconversion achieved and maintained undetectable viral load and virological failure occurred in only 1/50 people who started treatment within a year. However a closely monitored and supported primary infection cohort in San Diego reported that 29/48 (60%) changed therapy 61 times using a mean of 5 drugs over their first treatment year. Clinical and laboratory toxicity and treatment failure was responsible for 43% of these changes. Suppression to <400 and <50 copies/ml was reported in 52% and 21% patients at week 24 and 46% and 31% respectively at week 48. [13]

Goujard and colleagues reported on early onset of lipodystrophy in a French cohort of 121 patients treated in primary infection and who had been followed for >6 months. 22 patients (18%) presented with at least one lipodystrophy symptom after a mean 24 months follow-up and a cumulative risk factor was determined as 6% at 12 months, 18% at 24 months and 30% at 36 months. [14] The decision to initiate therapy early must therefore be sufficiently supported to avoid early development of resistance to drugs, and subsequent interruptions if followed must have some assurance of reversing adverse events.

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ON THE WEB

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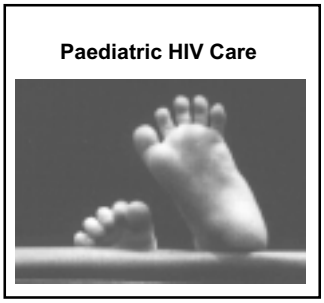

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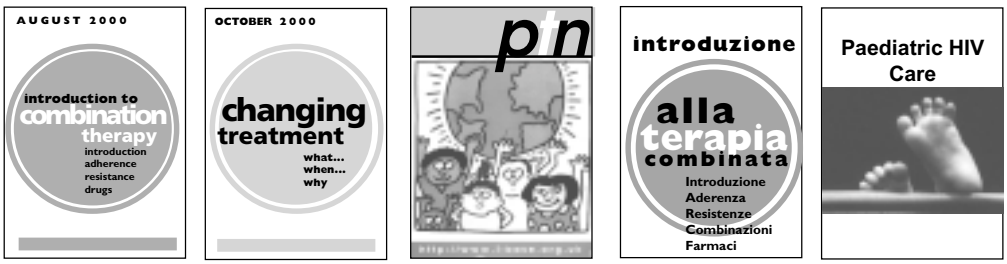

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