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TREATMENT ACCESS

Drug Companies' Spending on Advertising Doubled Research & Development in 2000

The nation's leading drug companies last year spent nearly twice as much on advertising alone as on research and development, and nearly three times more on advertising, administration and executive compensation, according to a study released Tuesday by Families USA, a not-for-profit health care consumer group.

The AP/Arizona Republic reports that the group said that the study's findings disputed the industry's "contentions" that the high cost of research and development has led to the recent rise in prescription drug costs, an argument that has also been used to justify the high cost of HIV/AIDS drugs, especially in developing countries (AP/Arizona Republic, 11/07).

The group analysed annual reports for fiscal year 2000 submitted by nine drug makers to the Securities and Exchange Commission. The companies — Merck, Pfizer, Bristol-Myers Squibb, Pharmacia, Abbott Laboratories, American Home Products, Eli Lilly, Schering-Plough, and Allergan — were selected because they produced the 50 most frequently prescribed drugs for seniors.

'Sugar Coating'

The study found that each of the nine companies except Eli Lilly spent more than double the amount on marketing, administration and advertising compared to research and development (Lilly spent 1.5 times the amount), while six of the nine "made more money in net profits than they spent on research and development last year."

Merck, for example, produced $40.4 billion in revenue last year — net profits represented 17% of this figure, 15% was spent on marketing, advertising or administration, and 6% was allocated on research and development, the latter percentage being the lowest of the nine companies. In percentage terms, Lilly spent the most of any company on research and development, 19%, while also seeing the largest net income at 28%.

The report also found "profligate spending on compensation packages" for pharmaceutical executives. For instance, excluding "unexercised stock options," Pfizer Chair William Steere received a compensation package of $40.2 million last year. "Pharmaceutical companies charging skyrocketing drug prices like to sugar coat the pain by saying those prices are needed for research and development," Ron Pollack, Families USA's executive director, said, adding, "The truth is high prices are much more associated with record-breaking profits and enormous compensation for top drug company executives".

Profits for People

The Pharmaceutical Research and Manufacturers of America criticized the study, saying that the report's "condemn[ation]" of drug makers was "unfair," the AP/Republic reports. PhRMA spokesperson Jackie Cottrell said, "When the pharmaceutical industry does well, patients do even better." She also cited industry figures showing that about $8 billion of the $15.7 billion that drug makers spent on marketing in 2000 was attributable to companies giving away free drug samples. "The system works — for patients. Because the pharmaceutical industry is profitable, Americans have the best chance in the world of getting the cure for Alzheimer's, cancer, diabetes or AIDS," Cottrell added (AP/Arizona Republic, 11/07). The complete Families USA report, titled, "Off the Charts: Pay, Profits and Spending by Drug Companies," is available online.
http://www.familiesusa.org/media/pdf/drugceos.pdf

http://www.arizonarepublic.com/business/articles/0711drugs11.html

http://www.phrma.org/

Source: Kaiser Network Daily HIV/AIDS Report
http://www.kaisernetwork.org/daily_reports/rep_hiv.cfm

Deal allows developing countries free access to journals

Six of the world's leading medical publishers have joined forces in a unique venture in which they have put profits aside to enable more than 100 of the poorest countries in the world to access vital scientific information free of charge through the internet. The BMJ's editor, Dr Richard Smith, described the arrangement, which is scheduled to start in January 2002, as "momentous" and one that will "completely transform the environment" in which health professionals, researchers, and policymakers in the developing world work.

Overseeing the signing of the "statement of intent" by senior executives of the publishers, Dr Gro Harlem Brundtland, director

general of the World Health Organization (WHO), said: “As a direct result of this arrangement, many thousands of doctors, researchers, and health policymakers, among others, will be able to use the best available scientific evidence to an unprecedented degree to help them improve the health of their populations. It is perhaps the biggest step ever taken towards reducing the health information gap between rich and poor countries.”

At the moment key medical journals, which can cost more than $3000 (£2100) for a year’s paper subscription, are simply beyond the reach of most institutions in developing countries. But when the tiered pricing scheme is introduced the least developed countries in the world will gain access to over 1000 of the top 1240 international biomedical journals free of charge. Slightly better off countries will be offered online access at a price that reflects national economies but still at a discount of 60-70%.

It is hoped that the initiative will give a clear signal to other industries, such as computer manufacturers and internet providers, to set up similar “ability to pay” schemes, said Barbara Aaronson, collection development librarian at the WHO. Smaller publishing groups, such as professional bodies that publish the New England Journal of Medicine and JAMA, are also expected to join the scheme.

Reliable internet access is still fraught with difficulties for many users in the developing world. Jon Conibear from Blackwell publishers described how students attending lectures of a visiting urologist in Addis Ababa vanished for two hours at 2pm the time that a satellite came within range to allow them internet access for two hours each day.

The WHO, which has spearheaded the project together with the BMJ and the Soros Foundations Network, also aims to provide training in communications technology as part of its Health InterNetwork project to improve public health.

Ref: BMJ 2001;323:65 (14 July) Source:
http://www.bmj.com

Nigeria to launch AIDS treatment program

Nigeria, Africa’s third most AIDS-ravaged nation, will on September 1 launch a pilot program to treat thousands of sufferers with Indian-made generic antiretrovirals in a joint program with the UN, officials said Thursday. “There is a project that starts next month with 10,000 adults and 5,000 children,” United Nations AIDS expert Mustapha Aliyu told AFP.

The project was announced in April, at the AIDS summit in Abuja, by Nigerian President Olesegun Obasanjo, Aliyu said. To that end, the Nigerian health minister several weeks ago negotiated the purchase of generic antiretrovirals from the Indian pharmaceutical company CIPLA, the UN said. Nigeria successfully negotiated a deal wherein they would pay 350 dollars per person per year for the drugs, a price heretofore only available to humanitarian organizations, said UN special envoy for AIDS in Africa, Stephen Lewis, after a tour through Africa. The Nigerian government will assume the entire cost of the treatment, Aliyu said.

The drug cocktails, which help slow the progression of HIV-infection, can cost between 10 and 20 thousand dollars per year per person in developed nations, and have until now been inaccessible to poor nations. Aliyu said the pilot program hoped “to encourage people to come forward and to be able to be tested for HIV. Experts believe that the lack of treatment options is one of the principal obstacles to voluntary testing for AIDS in African countries.

Africa is the continent most ravaged by the AIDS pandemic, counting 25.3 million people infected with HIV — comprising 70 percent of the 36.1 million AIDS sufferers worldwide. According to the UN, there are 2.7 million infected or HIV-positive Nigerians, putting the continent’s most populous nation third behind South Africa and Ethiopia.

Source: Agence France Presse

Europe Moves to Speed Up Approval of New Drugs

The European Commission has proposed accelerating the approval of new drugs, which could reduce by up-to-half the time it takes for new medication to reach markets and patients. The commission, an executive arm of the European Union (EU), also said it would slightly ease the ban on advertising prescription drugs, which should allow pharmaceutical companies to market some drugs directly to patients suffering from diabetes, AIDS and asthma. “Today’s decision will help patients all around Europe to get new and better medicines than is the case today,” said Erkki Liikanen, the commissioner for enterprise. “It will also help them get better information about the medicines available to them.” The announcement met a cautious welcome from drug companies like GlaxoSmithKline, Europe’s largest drug manufacturer. A spokesperson, Alan Chandler, said, “Any proposals that help patients get their medicines more quickly are to be welcomed.” Liikanen said a new “fast-track” approval procedure, based on that of the United States, could reduce the time for companies to win approval for drugs from 18 months to 9 to 12 months, shorter than the average 14-month approval process in the United States last year. The commission proposed that patents on drugs should be protected for a standardized 10 years in the EU before competitors

may seek permission to make a generic version.

Source: CDC NCHSTP Daily News Update

Trials of Immune Response Corp.'s AIDS Vaccine Remune May End After Pfizer Drops Financial Support

Pfizer Inc. notified Immune Response Corp. on Friday that it was pulling out of their collaboration on the AIDS vaccine candidate Remune sending Immune Response's stock "plung[ing]" and leaving the future of the vaccine candidate in doubt, the New York Times reports. The company's withdrawal, which Immune Response Vice President for Medical and Scientific Affairs Dr. Ronald Moss said "came out of the blue," could put an end to a clinical trial of the vaccine being conducted by Pfizer, a trial the Times said represented the "best hope of proving that the drug works." The pullout also leaves Immune Response with only $12 million in cash to further fund vaccine trials. Pfizer, which inherited the partnership when it acquired Agouron Pharmaceuticals, had already paid Immune Response $47 million and could have supplied an additional $30 million. Pfizer said it decided to terminate the partnership because Immune Response, founded by the late Dr. Jonas Salk, inventor of the polio vaccine, had not produced "convincing evidence" that Remune "helps patients" (Pollack, New York Times, 9/7). "Our decision was based on review of the data from several clinical trials. Our decision to withdraw ... should not be interpreted to mean that immune-based therapies as a class does not merit further investigation," Pfizer spokesperson Kim Simon said.

Trial Results Varied

Remune utilizes an approach "similar" to Salk's polio vaccine, using "inactivated" HIV to "bolst[er]" the patient's T-cell production (Dow Jones/Wall Street Journal, 9/7). The vaccine is not intended to prevent infection but is designed to help patients "keep the virus in check," the Times reports.

Some studies have shown Remune to "provoke" an immune response; however, they have not shown that the vaccine actually helps patients, and "many" scientists do not think using an inactivated virus offers the "best" hope for a successful vaccine. A trial involving more than 2,500 patients "failed to show that Remune improved survival or lengthened the time before HIV infection progressed to AIDS." Immune Response officials said that the trial coincided with increased use of new AIDS drugs, making it "nearly impossible" to "show a benefit over the placebo."

Last year, scientists accused Immune Response of attempting to "squelch" the publication of a scientific paper that described a failed clinical trial, and in 1995, the FDA "warned" the company "not to manipulate data" to show better results. Moss said that he was "puzzled" by Pfizer's reasoning to withdraw funding because new data, set to be presented Wednesday at an AIDS conference in Argentina, will show that the vaccine was effective in a "subset of patients with stronger immune systems."

Dr. Eric Rosenberg of Harvard Medical School said that the loss of funding could mean a "potentially good vaccine may not be adequately tested, and it deserves to be." Pfizer is "very foolish" to terminate the partnership, Dr. Fred Valentine, a professor of medicine at New York University, added. John McCamant, editor of Medical Technology Stock Letter, said he did not know where Immune Response could "go from here," citing the 44% drop the company's stock took Friday after the announcement. Pfizer's "no-confidence vote" could cause other potential investors to "balk," the Times reports (New York Times, 9/7).

Source: Source: Kaiser Network Daily HIV/AIDS Report
http://www.kaisernetwork.org/daily_reports/rep_hiv.cfm

CONFERENCE REPORT

1st IAS CONFERENCE ON HIV PATHOGENESIS AND TREATMENT

July 8-11, 2001, Buenos Aires, Argentina

Lipodystrophy and Metabolic Complications

By Andrew Carr, MD for HIVandHepatitis.com

Pathogenesis

David Cooper reviewed the pre-conference data on pathogenesis at a closing plenary. Although the data are clearly incomplete, his single theme was that all of the in vitro data and most of the clinical data implicate nucleoside analogues (NAs) and protease inhibitors (PIs), especially when used in combination. Although there is no case definition and early studies showed wildly varying prevalence rates, a case definition is pending and prevalence rates and risk factors identified in recent large studies strongly suggest that it is time to set aside the notion that we should do nothing because it may not be real, we don't know the cause, and "your drug does it but mine doesn't". There were some new data that did indeed improve our understanding.

A study by scientists at Bristol-Myers Squibb extended their previous data that stavudine (d4T), zidovudine (AZT) and ritonavir can indeed damage adipocytes in a dose-dependent and synergistic manner, although there was evidence (such as relatively unaffected ATP production and mitochondrial number) that this was not a result of damage to adipocyte mitochondria [Abstract 521].

Diagnosis

A thoughtful study from Belloso and colleagues looked at lipodystrophy diagnosis [Abstract 507]. They compared a more "sensitive" diagnostic model, which was based on the presence of only 1 patient reported change in body fat of any severity, with a less sensitive diagnostic model, which was based on at least 2 physical parameters identified by both clinician and patient. The latter diagnostic model was, as one would expect, less sensitive but far more specific. In particular, with the specific model but not the sensitive model cases and controls could be distinguished on DEXA scanning and laboratories. This is further objective evidence that a patient report of lipodystrophy on its own is fairly unreliable diagnostically, and that a patient report is reliable only if there are at least 2 affected sites and their physician agrees.

Prevalence and Incidence

The Vancouver group [Abstract 487] reported incidence rates of lipodystrophy of 35% in one year in patients on any therapy (the rate was somewhat higher in those receiving stavudine or a protease inhibitor), a higher rate than reported by the Spanish earlier this year in The Lancet. The regional rates for lipoatrophy, abdominal obesity and buffalo hump were 30%, 20% and 7%, respectively. Development of lipodystrophy was associated with a 50% greater risk of ceasing therapy (29%) than in those without, although it wasn't clear if lipodystrophy or other adverse events was the reason.

Treatment

Two studies reported on NA switching and surgery respectively. A pilot, randomised study from our group in Australia [Abstract 96] found that ceasing thymidine nucleosides (stavudine in 16 of 18 patients, all with undetectable plasma HIV RNA), with continuation of the remainder of the HAART regimen, resulted in an increase in limb fat from about 9% to 11% over a 6 month period. There are two disappointments from this study. Firstly, this increase, although statistically significant, still leaves the patients with very substantial peripheral lipoatrophy (a normal level in an adult man would be about 20-25%). Second, 5 of the 9 patients that ceased therapy had virological breakthrough, although 3 could be controlled with other agents.

On a brighter note, a French team [Abstract 500] found that autologous transplantation of fat resulted in objective and sustained (6 months) improvement in facial fat thickness and in appearance, as measured by patients (good or very good by 11 of the 15 patients), doctors, and independent observers.

Lipids

A chart review from an HIV endocrinology clinic in Houston found that statins (mainly atorvastatin and pravastatin) reduced total cholesterol by a statistically non-significant 13%, much less than would be expected in HIV-uninfected adults [Abstract 489]. This was not due to adverse events. In contrast, gemfibrozil, but not other fibrates, significantly reduced triglycerides

by 52%. No agent significantly increased HDL cholesterol, the most important lipid predictor of cardiac disease. A small switch study found that ritonavir-boosted indinavir (100/800 mg BID) had fairly equivalent effects on total and HDL cholesterol as indinavir 800 mg TID, but with a tendency to increase triglycerides. [Abstract 482]

Glucose Metabolism

A study from Peter Reiss' group in Amsterdam showed that a diabetic tendency in 6 men with lipodystrophy is a function of both peripheral and hepatic insulin resistance as well as increased hepatic glucose output. How much this was due to the drugs or the lipodystrophy or both is not clear [Abstract 495 - also in press at AIDS], although follow-up studies after protease inhibitor cessation are underway.

Vascular Disease

Diagnosis of hypertension in HIV-infected women was strongly associated with use of protease inhibitor therapy of greater than 2 years duration, after adjustment for other confounders such as obesity, race and age. [Abstract 512] Hypertension was not associated with plasma lipids, which suggests, but certainly doesn't prove, that protease inhibitors are not the culprit. However, it was not clear whether this increased diagnosis of hypertension was merely a result of more intensive blood pressure monitoring in such women, given the concerns of vascular disease in patients on therapy and because the rates of AIDS and AIDS-related mortality would have fallen substantially. Prospective regular measurement in patients on and not therapy are clearly needed.

Lactic Acidemia

An in vitro study [Abstract 95] reported that the peripheral white blood cells of patients with moderately symptomatic lactic acidemia had significantly lower amounts of mitochondrial DNA (mtDNA), when corrected for nuclear DNA (nDNA) content, than did antiretroviral-naïve adults or HIV-uninfected adults (mtDNA:nDNA ratios of 0.3, 0.7 and 1.3, respectively). The mtDNA levels increased after NA withdrawal and resolution of the illness. Whether mtDNA levels can predict symptomatic lactic acidemia remains to be seen. Given that lactate is an easy and very cheap way to diagnose the illness, the value of this test will be if it can predict future illness in asymptomatic patients on therapy. The authors could not explain why they found mtDNA levels to be lower in adults naïve to antiretrovirals, although there is limited data that HIV can impair mitochondrial function in cell culture.

Two studies of asymptomatic lactic acidemia [Abstracts 519 and 520] found very similar prevalence rates (9 and 11%) and risk factors (stavudine and lipodystrophy positively associated; abacavir negatively associated) to what has been reported at previous meetings. There was no data on management of, or on risk factors for, symptomatic lactic acidemia.

Hypersensitivity

Sub study data from the CHARM study (an ongoing randomised factorial study of zidovudine, lamivudine (3TC) and abacavir with either nevirapine, hydroxyurea or both) found that additional randomisation to prednisolone 40 mg daily for 2 weeks did not prevent hypersensitivity. [Abstract 92] If anything the risk was increased with prednisolone (hydroxyurea had no impact). The rash rate in the abacavir/nevirapine group was 20%, versus 6% in the abacavir/placebo group suggesting that most rashes were due to nevirapine not abacavir. However, the mean time to rash was 14 days in the prednisolone group and only 7 days in the placebo group, suggesting that some of the rashes may have been due to abacavir.

GlaxoSmithKline, in a review of 5332 patients who participated in abacavir studies of at least 24 weeks duration, found no factor that predicted the development of hypersensitivity to abacavir, except that black Africans appeared to have a lower risk. [Abstract 527] The rate remained relatively constant at 3.7%.

Hepatotoxicity

Two presentations, one from Boerhinger-Ingelheim, clarified the frequency, severity and risk factors for nevirapine hepatotoxicity. [Abstracts 44 and 45] Hepatotoxicity (increased ALT/AST greater than 3 times the upper limit of normal) occurred in 9% of HIV-infected adults with CD4+ T cell counts greater than 350 cells/mm3 within 6 weeks of commencing nevirapine, but only 3% of those with CD4+ T cell counts less than 200 cells/mm3. Hypersensitivity remains strongly associated with hepatitis B or C infection. Clinical hepatitis is rarer of course, about 3%. The authors suggested regular monitoring of liver enzymes.

References: Unless otherwise stated, all references in the text are to the 1st International IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires, Argentina.

Source:
www.hivandhepatitis.com

Lipodystrophy and Metabolic Disturbances

By Graeme Moyle, MD, MBBS for Hivandhepatitis.com

Metabolic and morphologic changes in persons receiving therapy are a key obstacle to the initiation and continuation of therapy, are stigmatising, and potentially place individuals at risk of future vascular morbidity. Whilst probable contributors to the aetiology of this condition have been described, the mechanisms by which these changes occur are not fully understood and no reliably effective therapy has been established.

Lipodystrophy Plenary

Issues with regard to lipodystrophy aetiology were summarised by David Cooper. [Abstract PL-11] In particular, approved protease inhibitors (PIs) appear to impact lipids and insulin resistance (including in healthy volunteers), affect adipocyte differentiation and hepatocyte lipid handling and release in vitro and interfere with the insulin-stimulated glucose uptake by GLUT 4 in adipocytes.

Data are less complete as to how nucleoside analogues (NAs) contribute although they have synergistic impact on adipogenesis (fat cell creation) and lipolysis (fat release) with PIs in adipocyte cultures in vitro. Diminished adipocyte mitochondrial DNA is difficult to interpret as it may reflect impending apoptosis rather than NA toxicity. Clearly, however, cohort studies implicate a role for NAs. Cross-sectional point prevalence studies suggest patients treated with NA + PI regimens have the highest rates of lipodystrophy with combined estimates of greater than 50% with these regimens.

Non-drug factors such as age, sex, disease severity, pre-therapy fat mass and exercise may also play a role in risk or severity. He also noted that a minority of studies have found associations with viral load and CD4+ cell count and that while immune reconstitution in transplant patients was associated with dyslipdaemia, insulin resistance and visceral obesity lipoatrophy was not described.

Mitochondrial Dysfunction

An in vitro study of NAs and PIs in adipocyte cultures looked at the impact of these drugs on fat cell metabolism and gene expression. Both mature and differentiating cells were evaluated over up to 19 days of culture. Both stavudine and zidovudine had no effects at physiologic concentrations (<10μM) but at exposure above 100μM adipogenesis (new fat cell formation) and triglyceride accumulation were suppressed.

Mitochondrial function did not alter significantly and total mitochondrial DNA did not alter with stavudine or zidovudine at exposures of 100-300μM up to 8 days. Changes in gene expression suggested alterations in genes involved in adipogenesis and lipogenesis but not mitochondria. [Abstract 521] This suggests that these agents are not exerting effects in fat cells via mitochondrial mechanisms.

Fat biopsies from patients with lipoatrophy, however, indicate declines in mitochondrial DNA and increased mitochondrial protein whereas these changes were not observed in untreated patients. These types of changes are seen in cells from persons with congenital mitochondrial diseases but may also be a pre-apoptotic event or a response to increased cell energy needs (such as seen in cold adaptation). The finding is suggestive of mitochondrial DNA problems in fat cells but not confirmatory. [Abstract 522]

A second study of fat biopsies from lipoatrophic areas in 10 HIV infected patients treated with HAART for 6 to 21 months was reported. In all 10 cases, adipocytes showed progressive disruption of cell membranes, fragmented cytoplasmic rims, irregular cell outlines, and eventually large fat droplets lying free in the connective tissue, consistent with apoptosis. In addition, many adipocytes showed variable compartmentalization of fat droplets, with decrease in cell size, and large, mitochondria-rich cytoplasm. These authors suggested that lipoatrophy is characterized by apoptosis, defective lipogenesis, and also an increased metabolic activity in many of the fat cells. [Abstract 494]

Lipids and Body Shape Changes

Considerable data with regard to both lipids and morphological changes were described in a large poster session on Tuesday afternoon, although limited new conclusions could be drawn. One key problem with assessing the aetiology of morphological changes has been that cross-sectional studies have tended to enrol individuals who have received multiple treatment regimens, thus compounding the potential for multi-factorial outcomes that are easily misinterpreted.

Effects of PI-based HAART

A study of 6 men with lipoatrophy receiving PI-based HAART were compared with six healthy male volunteers matched to their age and body mass index (BMI). Individuals were studied for insulin sensitivity using a hyperinsulinaemic euglycaemic clamp. Basal insulin concentrations were substantially higher in the lipoatrophic patients and mean endogenous glucose production 38% higher, basal lipolysis 78% higher in these individuals.

During the clamp procedure, endogenous glucose production was suppressed by only 50% in the lipoatrophic patients but by 85% in the controls. Whilst total glucose disposal increased in both groups, it only increased a modest 4% in the lipodystrophic patients compared with 23% in the controls. Lipolysis was also less efficiently depressed. Thus, patients with lipoatrophy appear to have both peripheral and hepatic insulin resistance and elevated glucose turnover. [Abstract 495]

ARV therapy and Lipodystrophy

A large cross-sectional study of 672 individuals on initial therapy was reported from a collaborative effort of 19 Spanish centres. Evaluating patients on first line therapy helps avoid some confounders or biases in cross-sectional studies. Patients were required to be on initial HAART regimens for greater than six months (mean 20 months) with body fat changes being evaluated clinically and categorised as facial lipoatrophy, abdominal adiposity or both.

Unfortunately, evaluation was not reported to be blinded to therapy. The study included 75% male and 25% female patients with a mean CD4+ cell count of 528 cells/mm3 and mean viral load of 2.2 log10 copies/mL. Patients were categorised by PI and NA regimen. Overall, 209 of 672 individuals were classified as having moderate to severe lipodystrophy. Overall, the rates of facial lipoatrophy (FA), lipoatrophy at other sites, abdominal adiposity (AA) and all lipodystrophy (LDS - atrophy and adiposity) did not differ across groups confirming that this is a class effect (Table 1).

Table 1:

Regimen	N	All LD	Facial Atrophy	Abdominal Adiposity
AZT+3TC+IDV	148	26%	8%	18%
AZT+3TC+NFV	67	25%	7%	8%
d4T+3TC+IDV	208	33%	13%	22%
d4T+3TC+NFV	121	29%	10%	15%
d4T+ddI+IDV	67	36%	15%	20%
d4T+ddI+NFV	40	24%	6%	12%

Observed lipoatrophy was as low as 6% (d4T, ddI plus Nelfinavir) and as high as 15% (d4T, ddI, plus Indinavir) suggesting an influence of PI choice rather than NA backbone over lipoatrophy. Combined lipoatrophy plus abdominal adiposity rates were lowest in individuals receiving d4T, ddI and Nelfinavir (24%) and highest in those receiving d4T, ddI, and Indinavir (36%). Time on antiretrovirals, the presence of hypertriglyceridaemia, and waste-hip ratio were amongst the independent factors associated with lipodystrophy in a multi-variate model, but no individual drug was associated with increased risk. [Abstract 486]

The Atlantic study provided data with regard to both fat redistribution and metabolic disturbances. These were ARV therapy naïve individuals given stavudine plus didanosine with either nevirapine, lamivudine or indinavir as the third agent. 298 individuals were randomised equally to the 3 regimens. Although no baseline evaluations were available, 150 questionnaires were completed by physicians with regard to the appearance of individuals within the study (indinavir 46, nevirapine 48, lamivudine 56).

The reasons and methods for this sub-selection were not reported. Patients were assessed for loss of fat in arms, legs, face and buttocks and fat gain in abdomen, neck or breast area. An additional 37 individuals underwent abdominal CT scan, a median of 121 weeks after enrolment. One of the problems with such an analysis lies in the fact that 238 individuals were randomised to the study and only 150 individuals have been evaluated and it remains unclear whether these individuals are necessarily representative of the overall population.

Fat accumulation, fat atrophy or both were reported in 16%, 35% and 15% respectively for individuals surveyed. No significant differences were observed between treatment groups and in the sub-set of individuals assessed by single slice CT scan, no differences in sub-cutaneous to total adipose tissue or visceral to total adipose tissues were observed. [Abstract 488] Lipid changes favoured nevirapine with rises in HDL-cholesterol being significantly greater with this agent (49%) relative to lamivudine (10%) or indinavir (16%) arms. Total:HDL-cholesterol ratio also significantly improved with nevirapine and lamivudine but not indinavir. Differences in triglycerides were not observed. [Abstract 496]

ARVs and Lipid Disturbances

The Combine study is another study of naïve patients randomised to either PI containing or sparing regimens (in this case on backbone of zidovudine and lamivudine). A cross-sectional study of individuals after 12 months of therapy was reported. This sub-study included 43 patients, 20 receiving nelfinavir, 23 receiving nevirapine. Consistent with the Atlantic study, HDL levels improved substantially with nevirapine but less so with nelfinavir. In both groups total cholesterol rose modestly. LDL rose significantly in nelfinavir but not nevirapine treated patients. Consistent with the Atlantic data the authors concluded regardless of NA backbone, PIs tend to lead to a more atherogenic lipid profile where as the use of nevirapine seems to lead to more lipid protected results. [Abstract 506]

Switching Therapy

With regards to treatment, the possibility of switching away from PIs or NAs has been raised as a means to managing this problem. Limited new information was presented with regard to switching away from PIs where available evidence suggest modest improvements in lipid parameters and generally good virologic control. Improvements in fat atrophy have not been consistently reported and no adequately powered studies have compared approaches.

A small pilot randomised trial evaluated thymidine analogue withdrawal in lipoatrophic patients, virologically controlled on PI-sparing therapy. Patients with lipoatrophy and viral load <400 copies/ml, who had replaced PI therapy with quadruple RT inhibitor therapy 6-12 months earlier either continued therapy or ceased either stavudine or zidovudine. Regional changes in body fat were assessed by DEXA scans at weeks 0, 12 and 24. Nineteen patients were enrolled, 10 to continue and 9 to cease stavudine or zidovudine. At baseline all 19 were on abacavir, nevirapine or efavirenz (18 / 1), stavudine or zidovudine (17 / 2) and lamivudine or didanosine (18 / 1).

At week 24, limb fat had increased modestly but significantly in those in the discontinue arm. Total body weight, central fat and lean body mass did not differ between groups. However, 5 of the 9 stop patients had viral rebounds whereas there were no virological failures that occurred in the continue-therapy patients. The authors concluded that this approach appears too risky for loss of virologic control, as with de-intensification studies in the past, hence different strategies to reduce NA burden need to be investigated. [Abstract 96]

A second small study evaluated the potential to replace stavudine with abacavir in 16 individuals who were followed for six months after therapy change. The only modification of therapy was stavudine to abacavir. All patients had lipoatrophy on entry to the study with completely virological suppression. The switch was associated with a significant decline in cholesterol but with no significant improvement in lactate, triglycerides or morphological changes. Two individuals (12.5%) experienced a virological rebound. [Abstract 491]

Conclusions

The impression from the lipodystrophy presentations was that we have some understanding of how PIs may cause metabolic disturbances but it remains unclear as to why fat cells are dying. The highest risk syndrome appear to be those involving PI plus NA but increasingly, evidence from evaluations of persons on first line therapy suggests that these problems are class effects with limited difference between drug choice.

References: Unless otherwise noted, all abstract references in the text are to the 1st International IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires, Argentina.

Source:
www.hivandhepatitis.com

Pharmacology at 1st IAS

Polly Clayden, HIV i-Base

The 1st IAS Conference on HIV Pathogenesis and Treatment took place in Buenos Aires, Argentina. As with any international HIV conference of merit, the ever increasing role of pharmacology was reflected in the number of posters, oral presentations and invited lectures, devoted to the subject. These included evaluations of drug-drug interactions particularly in the context of more complex therapies and an exciting glimpse into the future from Professor David Back who gave an overview of pharmacogenomics – the potential for truly bespoke prescribing?

Pharmacogenomics

David Back's began his presentation by reminding us that 'there's nothing new under the sun' and furnishing us with a brief historical overview of pharmacogenomics [1]. Starting with Pythagoras' recognition of the dangers of ingesting fava beans (indicating G6PD deficiency), he continued with benchmarks such as Mendel's rules of hereditary and the first time the term was coined (by Vogel in 1957), and then swiftly brought us forward to the present day and the more recent identification of polymorphisms in transporters.

He describes pharmacogenomics as 'the study of the genetic basis of the differences between individuals in responses to drugs in order to tailor drug administration to individual genotypes'. Genetic variability can alter both pharmacokinetics and pharmacodynamics of how an individual responds to a given agent. At present within HIV treatment, drugs are prescribed according to the tenet that 'one dose fits all'. Unfortunately a number of people do not respond to treatment despite taking their medication as prescribed, and others manifest unacceptable levels adverse events. He explained that adverse events are '

a major cause of morbidity and mortality with recent figures indicating this to be the fourth commonest cause of death in the USA.' Therefore the ultimate goal of pharmacogenomics must be to produce more personalised drug regimens tailored to the individual genotype in order to maximise benefit and minimise risk from existing drugs.

In relation to HIV and its treatment, the areas of particular importance are polymorphism in drug metabolising enzymes and transport molecules. Back suggested that the potential outcome of someone possessing either a poor or ultra-rapid metaboliser genotype will be reflected in their PK profiles and in turn their response to treatment. He discussed some of the polymorphic enzymes involved in drug disposition in relation to different ethnic groups and reported 'quite a lot of difference in ethnicity' [Fig.1]

Figure 1: Polymorphisms in genes involved in drug disposition

Polymorphisms in genes involved in drug disposition

	Phenotype	*Frequency*	*No. of Drugs*
Metabolism			
CYP2D6	Poor metaboliser Ultra-rapid metaboliser	White 6%, Oriental 1% Ethiopian 20%, Scandinavian 1.5%	>100
CYP2C9	Poor metaboliser		>60
CYP2C19	Poor metaboliser	White 4%, Oriental 23%	>50
N-acetyl transferase	Poor metaboliser	White 60%, Oriental 23%	>15
Thiopurine MT	Poor metaboliser	Low in all populations	<10
Transport			
P-glycoprotein	Reduced transport		>50
Binding			
α_1-AG	F1/A or S/A		

Another area of great interest - CYP 3A4 - the isoform involved in the metabolism of protease inhibitors and NNRTIs was until quite recently believed to have little variability among populations. It is beginning to emerge however, that the 3A4 system has several polymorphisms, Back explained that although the frequency and functional consequences of these variability's are still being determined, it would be fair to assume that variable expression of 3A4 will affect an individual's metabolism and may explain the range of interpatient variability of PIs and NNRTIs [Figs 2 and 3]. He summed up this part of the discussion with a recent quote from Gellner saying that '…the elucidation of genetic factors controlling a patients inducibility and activity of CYP3A could permit individual dose adjustments in therapies with its substrates and lead to identification of subpopulations with increased risk of developing toxicities.' [2]

Figure 2: CYP3A subfamily

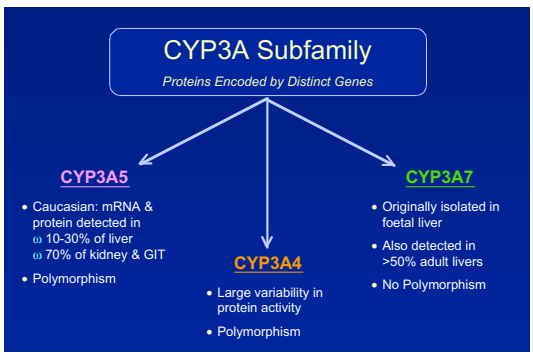

Figure 3: CYP3A4 polymorphism

CYP3A4 Polymorphism

Reported in both the *coding region* and *5' upstream regulatory region*

Allele	*Nucleotide Change*	*Effect*	*Allele Frequency*	
CYP3A4*1A	None (WT)	normal		
CYP3A4*1B	290A → G (non coding region)	some effect on substrate metabolism	African Hispanic Caucasians Chinese	30% 9.3% 3.6% 0.0%
CYP3A4*2	1280C → A	Ser 222 Pro (altered kinetics)	White Black Chinese	2.7% 0.0% 0.0%
CYP3A4*3	6981A → G	Met 445 Thr	Found in Chinese subjects	
CYP3A4*4 ↓ CYP3A4*15	Frequency and functional consequences being determined			

Therapeutic drug monitoring: a must for clinical practice?

In his lecture on Therapeutic drug monitoring (TDM) David Burger first described the rationale for its use in clinical practice. He also presented results from his own groups' ATHENA study of treatment-naive patients randomised to receive TDM or standard of care, (which we reported extensively in HTB XX) And from the French Pharmadapt trial of treatment-experienced patients, in which he examined limitations with the study design that could explain the negative findings ie no difference between the TDM and control groups.

He concluded that following the ATHENA results was sufficient data to recommend the use of TDM for indinavir and nelfinavir and that more data will be forthcoming over the next year or two.

Drug Interactions in HIV Medicine: How much do they matter?

For the third invited pharmacology lecture, Stephen Piscitelli explored the subject of drug interactions in treating HIV. He began by highlighting the dramatic changes that have occurred in this area of medicine over the past 5 years [5]. With the onset of PI use possible interactions were of a major concern to both patients and clinicians, they were considered a problem to be avoided and the role of the pharmacologist increased. He joked that at this time pharmacologists would '…follow patients around in case they ingested something that could have an interaction.' More recently however interactions, particularly with ritonavir to boost other PIs are exploited extensively for the patients' benefit in order to: improve adherence, increase drug levels, lower pill burden, improve convenience and lower costs. However he noted that although great strides have been made

in understanding the mechanisms and effects of interactions – the role of CYP450 isoforms, p-glycoprotein and other transporters and pregnane X receptor – much less attention has been paid to their management. In other words '…we can identify a problem but we're not so great at addressing them.

Several studies have shown what to expect when two drugs are administered together, but clinicians are unclear about how to then dose adjust to optimise their use. In addition evaluations of 2-drug interactions are not at all reflective of clinical practice and the '…paucity of multi-drug interaction studies provides little assistance to the clinician who is often left relying on observance of adverse effects or treatment failure s to whether a significant drug interaction has occurred.' [6]

He explained that there are serious limitations to evaluating HIV drug interaction literature, particularly that: it is such a rapidly changing field, that single or acute dosing studies may not accurately reflect steady-state conditions, that most studies identify an interaction rather than address a problem. He also urged that we evaluate the literature very critically as particularly with small studies, what appears to be an interaction many actually be interpatient variability.

In addition to interactions between antiretrovirals and other prescribed medicines Piscitelli also discussed the issue of herbal medicines, which are used widely by people with HIV in the US. To date his group has published two studies – one showing the effect of St John's Wort on indinavir (producing a 57% drop in indinavir levels), and another showing that garlic supplements decreased saquinavir levels by 51%. He also mentioned their as yet unpublished data, which shows no significant change in indinavir AUC after three weeks of co-administration with milk thistle.

For all agents though there are limitations to predicting drug interactions in individuals in clinical practice. Most in vivo and in vitro studies evaluate 2-drug regimens and the results may not be reflective of regimens used in patients particularly if they contain three or more drugs with opposing effects on CYP3A4.

As for the future, he recommends- improved drug interaction databases that are updated frequently (such as the University of Liverpool), more research into multi-drug interactions and better understanding of the effects of herbal medicines on antiretrovirals. In addition, TDM initiatives, 'If you could ever make a case for using this, its with a patient on 6or 7 drugs, and use of common sense. 'So we can do a better job at managing our patients'.

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Drug-drug interactions

Several PK posters looked at antiretroviral drug-drug interactions particularly within the context of more complex therapies.

Lopinavir/ritonavir dramatically decreases amprenavir levels

In order to evaluate the reciprocal interactions, in a retrospective study, Lamotte and colleagues determined Cmin in patients receiving lopinavir (LPV) and amprenavir (APV) in the presence of ritonavir (RTV) [1]. Cmin were measured in patients using lopinavir (LPV)/RTV (400/100mg BID) plus APV (450-750mg BID) plus or minus RTV (100mg BID) plus or minus efavirenz (EFV) (600 mg QD). The resulting APV Cmin were then compared to a reference group using APV (450 or 600 mg BID) plus RTV (100-200mg BID) plus or minus EFV (600mg QD) and lopinavir C-min to those in patients receiving LPV as the sole protease inhibitor. The investigators found that compared to the referent, APV Cmin were 49-83% lower when used in combination with LPV/RTV and they concluded that the 'LPV/RTV and APV combination did not seem to reach the expected APV Cmin for optimal antiviral efficacy on resistant strains and may compromise therapeutic response in salvage therapy'.

And negative drug-drug reaction between amprenavir and ritonavir…

It is well known that drug exposure of indinavir (IDV); saquinavir (SQV) and APV are increased by the co-administration of RTV. In a retrospective study from Guiard-Schmid and colleagues the influence of these three protease inhibitors on plasma levels of RTV were evaluated in patients using dual PI therapy [2]. RTV plasma levels were compared at Cmin and Cmax (2-4 hours post dose). All patients received 100mg RTV in combinations with either APV (600mg BID), IDV (200-800mg BID) or SQV (600-1000mg BID).

They found that in the APV group, Cmin and Cmax showed a lower inter-patient variability than in the other two groups. APV

Cmin values were found to be statistically independent of RTV plasma levels. In the IDV and SQV groups however, Cmin were positively correlated (p<01.01 and p<0.05 respectively) with RTV concentrations. As compared to the IDV and SQV groups, RTV plasma concentrations were found to be statistically lower in the APV group. In addition patients also using the NNRTI efavirenz (EFV) in the APV group did not experience any RTV concentration change as compared to those in the group not treated simultaneously with this drug (p=0.5). The PK profile of APV in the presence of RTV was unaffected by the administration of EFV.

These findings suggest a negative drug-drug interaction between APV and RTV. The investigators recommend that in a situation where a third PI is administered with an APV/RTV containing combination, TDM should guide dose adjustment to avoid treatment failure. They also recommend that if APV Cmin and Cmax are low, increasing the APV dose is preferable to modifying the RTV dose.

High inter-patient variability with lopinavir and ritonavir

Another retrospective study of experienced patients, from Meynard and colleagues, evaluated the Cmin of LPV and RTV in patients receiving this boosted PI (LPV/r) at a dose of 400/100mg BID without EFV or nevirapine (NVP) [3]. The RTV Cmin were then compared to a reference group receiving RTV (100mg BID) in combination with either APV (600mg BID), IDV (200-800mg BID or SQV (600-1000mg BID).

They found a 11-fold variability of LPV Cmin between people in the study group (median = 3172ng/ml, range 849 to 9298ng/ml). A positive correlation was found between LPV Cmin and RTV Cmin (p<0.0001), similar to that in IDV and SQV groups (p<0,01 and p<0.05 respectively). However in the LPV group the RTV median Cmin was significantly lower (134ng/ml, p<0.01) than in patients using either IDV or SQV (394ng/mg and 370ng/mg respectively) and APV caused a similar significant decrease in the RTV Cmin. In addition to the inter-patient variability of LPV Cmin, these data suggest a negative drug-drug interaction between LPV and RTV as reported between APV and RTV. The investigators also recommend the use of TDM to guide dose adjustment in patients receiving dual PI therapy (with or without other PIs) to prevent treatment failure.

Drug-drug interactions with tenofovir

Flaherty and colleagues from Gilead Sciences evaluated the PK parameters of tenofovir DF (TDF), IDV, LPV/r and EFV in a steady state study in a group of healthy volunteers receiving the agents alone or in tenofovir containing pairs [4].

The study was a three way crossover design – within each of three cohorts each subject received all of the following treatments - Treatment A: TDF (300mg QD) alone; Treatment B: TDF and IDV (800mg every eight hours), LPV/r (400mg/100mg BID) or EFV (600mg QD); Treatment C: IDV, LPV/r or EFV alone. All doses were given in the fasted state except for the LPV/r cohort where all drugs were administered with food. Multiple blood samples were taken over 24 hours following the last (morning) dose of study medication in each period and PK parameters including AUCs and Cmax were calculated.

Tenofovir PK were unaffected by co administration of EFV or IDV. AUCs and Cmax ratios (90%CI) [0.96 (0.85,1.08) and 1.07 (0.94,1.22)] for EFV and (90%CI) [1.07(0.95,1.19) and 1.14 (0.97, 1.33)] for IDV. Coadministration with TDF had no effect on the AUCs and Cmax of EFV [0.96 (0.93,1.0) and 0.96 (0.91, 1.02)] or IDV [0.95 (0.82, 1.82, 1.10) and 0.89 (0.70, 1.12)]. Tenofovir AUCs and Cmax were approximately 30% higher during administration with LPV/r [1.34 (1.25, 1.44) and 1.31 (1.12 and 1.53)]. Coadministration with TDF resulted in 155 lower LPV AUCs [0.85 (0.78, 0.93)] and Cmax [0.85 (0.77,0.94)] and 11% lower Cmin [0.89 (0.78, 1.01)] - this change in the Cmin is not considered to be statistically significant.

The authors concluded that coadministration of tenofovir DF with IDV or with EFV does not result in clinically relevant drug-drug interactions and that the small changes observed in LPV PK parameters when administered with tenofovir DF are not expected to have clinical relevance.

A second Gilead study from Kearney and colleagues with the same crossover trial design investigated the PK parameters of TDF, lamivudine (3TC) and didanosine (ddI) when administered to healthy volunteers alone or in TDF-containing pairs [5].

In this study, Treatment A: TDF (300mg QD) alone; Treatment B: TDF and 3TC(150mg BID) or ddI (400mg or 250mg<60kg QD); Treatment C: 3TC or ddI alone. All doses were administered in the fasted state over seven days to achieve steady state with a seven-day washout period between treatments. ddI was taken one hour prior to TDF during the period of coadministration. Multiple blood samples were obtained and PK parameters were assessed as in the previous study.

The investigators found that coadministration with 3TC did not affect the PK of tenofovir [mean ratios (90% CI) for AUCs 0.96 (0.85. 1.08) and Cmax 1.02 (0.96. 1.09)]. Similarly there were no significant alterations in tenofovir PK when taken with ddI [AUCs 0.94 (0.86, 1.02) and Cmax 0.98 (0.82, 1.12)]. Coadministration of TDF with 3TC produced a 0.9 hour delay in Tmax of 3TC and a corresponding 24% decrease in Cmax [0.76 (0.66, 0.88)], but no difference was reported in overall drug exposure [AUCs 0.97(0.82, 1.15)]. However ddI Cmax was increased by 28% [1.28 (1.11, 1.48)] when taken with TDF and overall exposure increased by about 40% [AUCs 1.44 (1.31, 1.59)].

They concluded that coadministration of TDF with 3TC does not result in clinically relevant drug-drug interactions. Coadministration of ddI with TDF did not affect the PK of TDF but increased ddI exposure by 40%. However their assessment

of available data did not suggest an increased risk of ddI adverse events when ddI is administered with TDF.

Drug-drug interactions with PIs and NNRTIs

A study from Caldwell and colleagues showed data that evaluated the prevalence of confirmed and potential drug interactions within a group of 229 patients. In addition the outcomes of the confirmed interactions were determined [6].

This group of patients who were receiving either a NNRTI and/or PI (or had done so previously) were evaluated for confirmed and potential drug-drug interactions. They described 'confirmed drug interactions' as drug interactions either identified in the manufacturer's prescribing information or within existing data, and 'potential drug interactions' were those identified in the manufacturer's prescribing information as warnings or cautions without specific recommendations.

A total of 411 NNRTI and/or PI containing regimens were identified within this cohort. 449 confirmed and potential interactions were identified, of which 160 could be classified as confirmed drug-drug interactions. Out of these 160 confirmed drug interactions identified, 100 were identified as synergistic interactions, ie pharmacokinetically 'boosted' PIs. In addition six different non-antiretroviral drug-drug interactions (n=41) were also identified with no negative outcomes.

Three patients receiving saquinavir and efavirenz within their regimens did not achieve virologic success, which could have been attributed to the drug-drug interaction.

The investigators concluded that 'With pharmacist involvement, only 1.9% of the confirmed interactions were potentially associated with negative outcomes despite a 14.6% prevalence rate of confirmed drug-drug interactions (excluding synergistic reactions) in patients receiving PIs and NNRTIs'.

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Immuno-therapy at the 1st IAS Conference

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The First International AIDS Society Conference on HIV Pathogenesis and Treatment was laden with new information on immunotherapy of HIV specifically concerning interleukin-2 (IL-2). Whilst several recent additions to the antiretroviral armamentarium got a good airing most studies of drugs were longer term follow-up of already presented data. When it came to interleukin-2, the most advanced of the immunotherapeutic agents there was a wide range of studies that which increased both clinical knowledge as well as basic science.

The French have always been great proponents of this approach from the early years of the epidemic and this perhaps the more balanced European view that the immune system is as vital, if not more vital than the virus in terms of a therapeutic target.

IL-2 Raises CD4s in Patients with <200 CD4s to Over 200 CD4s

Christine Katlama from the Hopital Pitie Salpetriere in Paris presented week 80 data on the ILSTIM study (ANRS 082) [1]. In this trial patients who still had less than 200 T4 cells after 6 months of HAART were randomised to receive 4 cycles over 24 weeks of IL-2 (4.5 MIU twice daily for 5 days). The idea of the study was to establish if IL-2 as an additional treatment could raise the T4 count out of the under 200 danger zone to potentially reduce the likelihood of opportunistic infections. After week 24 all patients could opt to take cycles of IL-2. Seventy-two subjects with a median HAART duration of 19 months entered the study of whom 31 received IL-2 therapy. The median age was 45 with pre-HAART T4 levels of 65 which rose after treatment to 145 (15% were <100 at baseline). During the first 24 weeks a statistically significant rise in T4 cells occurred in the IL-2 group compared to the HAART alone group (220 versus 138 $p<0.0001$) with 81% versus 33% achieving greater than 200 T4 cells. By week 80 the median T4 cell level in the IL-2 arm was 380 with 93% over 200 whilst the delayed IL-2 arm had increased to 270 with 83% over the 200 T4 cell threshold. This median increase of almost 250 T4 cells was achieved with an average of 10 cycles of IL-2. The speaker was asked a question as top whether there was any clinical benefit to this treatment and

responded that the study although not designed to assess this had raised T4 cell levels into a range at which clinical disease was less likely. In addition there were clinical endpoints studies (SILCAAT and ESPRIT) that were ongoing and designed to address this issue.

Tolerability of IL-2

Albert Wu from Johns Hopkins University in Baltimore then presented quality of life data from the ACTG328 study that evaluated 150 subjects on HAART for 12 weeks [2]. They were randomised to receive HAART alone (51), cycles of intermittent subcutaneous (SC) IL-2 (54) or cycles of continuous intravenous (CIV) infusion IL-2 (55) every 8 weeks for 52 weeks. The study used an ACTG quality of life (QOL) tool with 21 elements that addressed general well being, pain, energy, social functioning, physical functioning and several other areas of health. Subjects were assessed at baseline, and at days 0 and 5 of cycles 1, 3 and 6 (approximating weeks 16, 28 and 52). Whilst no significant changes were seen at week 16 by weeks 28 and 52 subjects in the SC IL-2 group scored significantly better on certain elements and the summary score for this group was better than for either for the other groups ($P<0.05$). The QOL of subjects receiving IL-2 dipped at days 5 as would be expected since the symptoms of IL-2 treatment are well documented with fever, bodily pain and flu-like symptoms. However the decrease in QOL scores diminished over time suggesting that either patients became used to coping with the side effects of IL-2 or that the management of side effects was better. Wu pointed out that although not a clinical endpoint study these data were the first to assess the tolerability and effect on QOL of IL-2 in a randomised fashion which may be of greater significance to the patient than the incidence of new AIDS defining events.

Preliminary Data Suggests IL-2 Stimulates Thymus

Several investigators presented information as to the effects of IL-2 on various areas of the immune system. Brigitte Autran gave an elegant talk on her studies of patients in ILSTIM attempting to ascertain the action of IL-2 on thymic function [3]. She examined 13 subjects from the ILSTIM study over 80 weeks by measuring naive T cells and signal joint T-cell receptor excision circles. These are the by products of part of the alignment of the immune system in response to particular foreign material during the development of immunity. It would appear from the work that Autran presented that the effect of Il-2 is to stimulate the activity of the remaining thymus in HIV infected subjects leading to an improved immune capacity. This is good news at it suggests that this agent can re-teach the immune system in a way that will produce persistent benefits form intermittent therapy.

Does IL-2 Induce HIV Replication?

One concern that as been voiced is that the use of IL-2 in the absence, or even the presence of antiretroviral medication may induce viral replication and thereby either establish a new set point of HIV viraemia or speed progression of HIV disease. Anne Sullivan presented data from the UK-Vanguard IL-2 study in which 36 subjects with CD4 cell counts >350/cumm were randomised to receive no treatment or IL-2 at two dosage levels (3 cycles of 4.5MUI or 7.5MIU twice daily for 5 days at 8 week intervals over 24 weeks) [4]. She showed data on markers of T cell activation (CD38) as well as markers of IL-2 receptors (CD25). No sustained rises in either occurred although transient blips per cycle were observed that paralleled the rises in viraemia that have been seen previously. This is important in the sense that further immune activation is seen as disadvantageous and that previously several groups have reported CD38 levels to be an independent predictor of progression in HIV disease.

So all in all there was plenty of new data to suggest that intervening with at least IL-2 may be a good therapeutic strategy. This agent is now available in France for subjects CD4 cell counts less than 200/cumm through a government sponsored program although the licensed indication has not yet been changed.

Remune

Remune has not fared as well and as the conference closed Pfizer announced they were closing the development program with the Immune Response Corporation (IRC) thereby putting the continued research of this agent in jeopardy. With no clinical endpoint data and limited evidence of any surrogate marker changes in studies so far conducted it seems unlikely that this will go ahead.

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Entry Inhibitor Updates from the 1st IAS

Mike Youle, MD for HIV i-Base

In addition to the plethora of good news on immunotherapy, attempts to block entry into the cell by HIV also got significantly favourable press. In his round-up of new antiretroviral agents in late stage development, Rob Murphy from Northwest University in Chicago, noted the advancing potential of the fusion inhibitors T20 and T1249. Although these drugs have to be given intravenously tolerability is relatively good and no significant safety concerns have arisen to date. New information on T20 came from Cal Cohen of the Community Research Initiative, Brookline MA, USA [1]. Fifty-five subjects single arm roll over Phase II study completed quality of life questionnaires at baseline and week 48. The majority of respondents agreed that subcutaneous T20 did not limit surveyed activities and approximately two-thirds (62%) reported the T20 injections and similar in convenience to other HIV/AIDS drugs. Of the patients completing 48 weeks of the treatment 98% would choose to continue T20 and 85% rated the ease of injection as not bad to very easy. This is good news since the injection schedule had been deemed the major problem likely to limit the utility of this agent.

Jay Lalezari from San Francisco showed data from 20-208 that evaluated the plasma pharmacokinetics of three formulations of T20 [2]. Forty-eight subjects received T20 as either 75mg/mL or 100mg/mL formulations with carbonate or TRIS buffers for 14 days and then were switched to the standard 50mg/mL. The Cmax and area under the curve (AUC) for the newer 100mg/mL (90mg deliverable) form showed no difference from the current form and will result in a reduction in injections to one twice daily.

In a session that drew the glitterati of entry inhibitor researchers together, Joe Eron from Chapel Hill NC, USA presented an overview of fusion inhibitors that focused on T20 and T1249 []. Studies of the former have shown at least a 0.5log110 drop in HIV RNA in subjects highly resistant to other antiretrovirals and phase III studies are ongoing. A dose response appears to be present but resistance does develop in some subjects. Study T124-101 evaluated 61 subjects who received drug from 6.25mg to 50mg once daily exhibiting a 0.6-1.2log10 reduction in viral load. T1249 extends to the high affinity (deep pocket) region of gp41 and therefore theoretically should be more active than T20. It also should be available as a once daily injection. In isolates already resistant to T20 T1249 worked in vitro and would be assumed to have some effect in vivo. Eron raised concern over the feasibility of long-term administration of these injected agents, about resistance profiles, antibody formation and manufacturing capacity.

Cecile Tremblay then gave a summary talk on co-receptor blockers that commenced with some impressive computer graphics to demonstrate the complexity of virus-cell receptor interactions [4]. Entry into a target cell involves specific recognition of two surface cell molecules (CD4 and CCR5/CXCR4) by the membrane spanning, trimeric glycoprotein (Env) spikes of the virion. Key stages in the entry process – interaction of gp120 with CD4, conformational altered gp120 with the co-receptor molecule and the protein-protein membrane-binding interaction – are postulated to be novel targets for therapeutic intervention. There are several co-receptor molecule analogues currently under investigation by several companies and exist as CCR5 inhibitors such SCH-C and SCH-D and CXCR4 blocking drugs such as TAK-779 and AMD3100. The use of these agents together with fusion inhibitors would be logical since a combination approach with antiretrovirals has shown significant benefit over mono- or dual therapy. Also preliminary data suggest that interactions between various attachment/entry inhibitors might e dependent on multiple factors including polymorphisms in the envelope of HIV-1 clinical isolates, the expression (both quantitative and qualitative) of the co-receptors on host cells as well as pharmacokinetics. Tremblay presented work done by her in Martin Hirsch's laboratory, at Massachusetts General Hospital showing marked synergism between all tested antiretrovirals and SCH-C and T20 and between T20 and TAK-779 or SCH-C. It would appear that combination of agents might improve potency and potentially prevent co-receptor switch, although it has been suggested that this is unlikely in vivo.

Bahige Baroudy from Schering-Plough Research showed exciting data from the two lead compounds from this group SHC-C and SCH-D [5]. These CCR5 blockers can be made as oral formulations, a huge advantage over the only agent to reach the grade at the moment T20. He showed the complex series of assays and screening tests that had produced these two lead compounds. The SCH-C studies were put on hold early this year as in the first studies a prolongation of the Q-T interval was seen on the electrocardiograms (heart tracings) of subjects given the higher doses of the drug. This could be an early marker of heart toxicity of the agent and needed a thorough evaluation by the regulatory agency the FDA before they would allow further studies. This has now been completed and the drug is being moved into more advanced development. SCH-D is likely to take over as the prime drug to be developed and he presented data showing this to be a stronger agent with a half life in the blood of 6 hours and which had been tested for toxicity in animals. Definitely a drug to watch.

A further therapeutic target on the cell surface that is under investigation is DC-SIGN which was thoroughly reviewed by Vankooyk from the University Medical Centre, Nijmegen, the Netherlands [48]. This is a novel dendritic cell-specific lectin that acts as a surface receptor. It captures HIV through a mannose dependent interaction with gp120. Dendritic cells (DC) capture organisms then enter the periphery such as the skin and mucous membranes and take them to the secondary lymphoid tissues where they present them in an antigenic form and thereby initiate some immune response. As such this interaction is important to deliver HIV to lymph nodes and could be a target for HIV intervention. An additional similar receptor, called L-SIGN has recently been identified raising the likelihood that multiple of these receptors will be found and that a combination blockade approach may be necessary.

Finally Mark Wainberg from McGill University AIDS Centre in Montreal, Canada gave an excellent talk on potential new areas for drug development that spanned the totality of the virus life cycle [7]. It included discussion of targets such as de-stabilisation of the viral nucleocapsid protein, affecting RNAase H activity and more carefully examining the capacity to affect the tat gene. One group, from the Karolinska Institute in Stockholm presented data on novel tri-peptides GPG-NH2 and ALG-NH2 that interact at the carboxyl terminal and result in an arrest of the budding process [8]. GP-NHS is current in phase II studies.

So overall a fascinating array of new agents that can be used to block the entry into cells by HIV. What will be even more interesting is to see how these compounds can be used to treat HIV in combination with the currently available drugs and what benefit and toxicity this may result in.

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Structured Treatment Interruptions (STIs) and Structured Intermittent Therapy (SITs)

By Mark Dybul, MD for

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The 1st IAS Conference on HIV Pathogenesis and Treatment in Buenos Aires, Argentina had numerous oral and poster presentations on approaches to treatment interruptions. There were updates on auto-immunization strategies as well as new insights into the important issues of toxicity and resistance.

The three main strategies of treatment interruption were well represented for 1) auto-immunization in patients treated with HAART during acute or chronic HIV infection, 2) reducing the amount of time patients receive HAART and 3) allowing reversion to wild type in salvage therapy.

Auto-immunization in Acute HIV Infection

Bruce Walker [Abstract 139] provided an update of the work being done in his group with 14 individuals who were treated during acute HIV infection: nearly all patients were begun on HAART prior to developing a positive HIV ELISA. All individuals achieved and maintain a viral load below the limit of assay detection for a mean of approximately 1 year prior to beginning structured treatment interruptions (STIs). In this strategy, patients resume therapy if their plasma HIV reaches greater than 5,000 copies/mL on 3 measurements or greater than 50,000 copies/mL on a single measurement.

To date, these 14 individuals have undergone between 1 and 4 treatment interruptions. Only 2 individuals were termed 'failures' or individuals who have not had clear changes in viral dynamics following multiple STIs. In contrast, several individuals have remained off therapy for greater than 1000 days following 1-3 STIs with plasma viraemia less than 5,000 copies/mL and relatively stable CD4+ T cell counts.

However, Dr. Walker noted that in a small number of patients, there may be a slow decline in CD4+ T cell counts that requires monitoring. Of interest, 2 patients who developed relatively high rebounds of greater than 20,000 copies/mL after several hundred days off therapy had spontaneous declines in viral load back to less than 5,000 copies/mL without therapeutic intervention.

During a presentation focused on other aspects of treatment interruptions, Anthony Fauci [Abstract PL4] presented new data from their group on 6 individuals who had begun therapy during recently acquired HIV infection, i.e., within 6 months of infection. These individuals had participated in a pilot study comparing 4-drug HAART using stavudine, lamivudine, indinavir and efavirenz alone or in combination with 3 cycles of subcutaneous interleukin-2 (IL-2) during the first 12 months of therapy.

In this extension of that study, 3 individuals from each arm elected to undergo treatment interruptions, resuming therapy if plasma viraemia exceeded 10,000 copies/mL on 3 measurements or 50,000 copies/mL on one measurement. None of the patients received IL-2 during the treatment interruption phase of the study. Of these individuals, 1 patient remained off therapy for 6 months after the 1st interruption with plasma HIV RNA less than 5,000 copies/mL. Three patients, who met virologic criteria to resume therapy with the first interruption, experienced a prolonged period to rebound with the second interruption

and a significant decrease in the peak plasma viraemia from the first to the second interruption. One individual had similar peak viraemia and rebound kinetics from the first to the second interruption and one had only undergone a single interruption that met failure criteria.

There was no apparent difference between those individuals who had or had not received IL-2. Thus, patients treated within 6 months of infection may have responses similar to those treated during acute HIV infection.

Both Drs. Walker and Fauci emphasized that there is no direct clinical applicability to these data and that the risks of resistance and immunological damage from this strategy require further evaluation. However, the results do lead to important avenues of research in terms of the components of immune control of HIV infection.

Auto-Immunization Chronic HIV Infection

Franco Lori [Abstract 56] briefly presented data from an STI study in which monkeys underwent cycles of 3 weeks on HAART followed by 3 weeks off HAART for 3 cycles. This strategy did not result in a change in peak viraemia or the kinetics of viral rebound regardless of whether the regimen included hydroxyurea. He then went on to present data from a human study with a similar schedule. Sixty patients who were previously antiretroviral naïve with CD4+ T cells greater than 200 cells/mm3 and a viral load greater than 5,000 copies/mL were randomised to receive didanosine, stavudine and either indinavir or hydroxyurea for 12 weeks.

Following the initial 12 weeks, patients were further randomised to undergo 4 cycles of structured treatment interruption (STI) according to a fixed schedule of 3 weeks on therapy followed by 3 weeks off therapy or to remain on continuous therapy. At the end of a 36 week interval, patients in both arms interrupted treatment for a final 3 weeks period. In the STI arm the mean rebound viraemia with each of the 4 off periods was unchanged, and there was no difference between the groups treated with hydroxyurea or indinavir. Plasma HIV RNA was 172 and 70 copies at the end of the 36 week period (the last on-treatment period for STI).

During the final off-HAART period, there was rebound viraemia in both the STI and continuous HAART groups; statistical analyses had not yet been performed. Thus, there was no evidence for auto-immunization in this study.

Less Time on Drugs

In his plenary lecture, Anthony Fauci [Abstract PL4] provided an update on the work being done in his group on what they call structured intermittent therapy (SIT) to differentiate it from "auto-immunization" approaches. The NIH team, of which the author of this article is a part, has been studying both long cycle, 2 months off HAART followed by 1 months on HAART, and short cycle, 7 days on HAART followed by 7 days off HAART, SIT. Fifty-two patients have been enrolled in the long cycle study: 26 receiving intermittent therapy and 26 receiving continuous therapy.

All of the patients had a viral load less than 50 copies/mL and CD4+ T cell counts greater than 300 cells/mm3 at enrolment with equivalent pre-HAART CD4+ T cell counts and viral loads between the groups. From the first to the second, third and fourth interruptions of 1 month among 22 patients, there was a mean log difference of 0.6, 0.3 and 0.5 log10 copies/mL, respectively. After up to 6 cycles in some patients, by 8 weeks back on HAART, all patients had a viral load less than 500 copies/mL, and most had a viral load less than 50 copies/mL.

Dr. Fauci also provided an update on the group's novel strategy of short cycle intermittent therapy. Eight patients receiving stavudine, lamivudine and indinavir/ritonavir in cycles of 7 days on followed by 7 days off for 8-15 months maintained suppression of plasma viraemia; all determinations are done after the on-HAART period. Several patients experienced infrequent low-level 'blips' of 52-350 copies/mL. In addition, Fauci reported that during 6 months in 5 individuals, and 12 months in 3 individuals, there was no evidence for a significant increased in HIV replication by several virologic and immunologic assays including lymph node evaluations in 5 patients.

Resistance

Dr. Fauci reported that despite re-establishing virologic control during the 8 weeks on-HAART period, 4 patients receiving long-cycle intermittent therapy developed genotypic and phenotypic resistance to efavirenz (K103N) and/or Lamivudine (M184V) during the 4th to 6th cycle of treatment interruptions. Interestingly, all of the patients who developed resistance had relatively high levels of plasma viraemia during the off drug periods.

Dr. Fauci also showed data from 4 individuals receiving efavirenz who have had high level rebound viraemia but have not developed resistance; although in some cases the levels of plasma HIV RNA were too low to perform standard resistance testing. Dr. Fauci concluded that at this point NNRTIs can not be recommended for treatment interruption strategies that are conducted for long intervals of time and that may, therefore, result in significant rebound plasma viraemia. There was yet no evidence for the development of resistance in patients receiving protease inhibitor-based regimens.

In addition, Zala and colleagues presented data [Abstract 142] in 14 individuals treated within 6 months of acquiring HIV infection who received stavudine, didanosine and nevirapine with or without hydroxyurea for a mean of 54 weeks. Patients were subsequently offered sequential treatment interruptions. In 6 of 9 patients who had genotypic analysis done (VIRCO)

during the peak of viraemia during the first interruption, there was evidence for resistance to nevirapine (K103N, 190A, Y181C).

As in the data presented by Dr. Fauci, the development of resistance was not suggested by clinically significant virologic failure. In addition, there were several reports of individuals participating in STI studies who developed resistance to Lamivudine while receiving PI-containing regimens.

In regards to short cycle SIT with cycles of 7 days off and 7 days on HAART, Dr. Fauci reported that here was no evidence for genotypic or phenotypic resistance as determined by the VIRCO assay out to 12 cycles in 8 individuals; since the patients had such low plasma viraemia the virus for the assays was obtained by inducing it from activated CD4+ T cells. As noted above, while none of these individuals were receiving nNRTIs, all were receiving Lamivudine.

There is clearly a risk to developing resistance to nNRTIs and lamivudine with treatment interruption strategies that utilize relatively long intervals off therapy. Further evaluation of this risk is required.

Toxicity

Reporting the data on the NIH study of short cycle HAART, Dr. Fauci showed that at 24 weeks of SIT, there was a significant decrease in total cholesterol, LDL and triglyceride levels (all with p=0.001). These decreases were maintained out to 52 weeks in the 3 patients who had been on study longer.

Conclusions

It is clear that there are differences in responses to treatment interruption strategies in patients who began HAART during acute and possibly recently-acquired HIV infection, compared to patients who began HAART during chronic HIV infection.

A significant proportion of individuals who begin therapy during recently-acquired HIV infection seem to be capable of controlling HIV plasma viraemia during 1-4 STI cycles, while only a small minority of individuals who begin therapy during chronic HIV infection seem to have a similar result.

Understanding the mechanisms of viral control may provide important insights for future therapeutic options and vaccine strategies. However, at this point there is no clear clinical applicability to STI in either acute or chronic HIV infection and STI for auto-immunization cannot be recommended outside of a research setting.

Regarding treatment interruptions for salvage therapy, the data presented at the meeting corroborates previous findings that there is a clear risk to patients in terms of enhanced HIV viraemia and significant declines in CD4+ T cell counts. Given the low levels of CD4+ T cells in individuals in the salvage situation, this strategy also was not recommended outside of a research setting by any of the presenters.

Finally, in terms of intermittent therapy with the sole purpose of reducing total time individuals receive antiretroviral drugs, approaches that use relatively long cycles of interruptions, and therefore lead to relatively high rebound plasma viraemia in many individuals, may pose a significant risk for the development of drug resistance. This was especially true for patients receiving regimens that included nNRTIs and Lamivudine.

The relative risk to individuals receiving PI-containing regimens is unknown. Despite the development of resistance, patients seem to be able to re-establish virologic control and CD4+ T cell counts during the on-HAART periods. This approach requires further investigation.

In contrast, there was no risk of developing resistance at up to 52 weeks (26 cycles on and off therapy) in patients who received short cycle intermittent therapy of 7 days on HAART followed by 7 days off HAART. In addition, 10 patients maintained suppression of HIV in the peripheral blood and lymphoid tissue while preserving CD4+ T cell counts for up to 64 weeks of intermittent therapy. These individuals also had significant decreases in markers of toxicity.

However, it is important to note that this a relatively small number of patients with relatively high CD4+ T cell counts who had done very well on HAART for a long period of time prior to SIT. In addition, all patients received the same double PI-containing regimen.

Thus, for these approaches larger, randomised, controlled clinical trials are necessary and they cannot be recommended in clinical settings. Finally, analyses of the data may provide important insights into the replication kinetics of rebounding HIV.

References: Unless otherwise stated, all references in the text are to the 1st International IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires, Argentina.

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Adverse Events with Antiretrovirals

By Graeme Moyle, MD, MBBS

Several areas of interest exist regarding the management and risk of toxicity with antiretroviral (ARV) therapy. These include concerns regarding liver dysfunction, bone changes, lipid and insulin disturbances, and gastrointestinal (GI) effects. Changes in fat deposits with therapy are discussed in separate reports.

Liver Disease and Antiretrovirals

With the growing number of individuals co-infected with hepatitis B or C, concern regarding the potential for antiretroviral agents to trigger or worsen hepatic disease has risen. Additionally, antiretrovirals themselves may cause hepatic dysfunction. The concern regarding hepatotoxicity is greatest with some non-nucleoside reverse transcriptase inhibitors (nNRTIs), although the rare syndrome of lactic acidosis with hepatic steatosis is principally related to nucleoside analogue (NA) therapy.

Possible mechanisms through which therapy may lead to liver problems include 'idiosyncratic' reactions and direct injury by cytotoxins. Idiosyncratic reactions are generally of a low incidence and may result from drug allergies, such as to nNRTIs, sulphonamides or to metabolites of isoniazid. Many cytotoxic agents may be used by persons with HIV. These include non-steroidal anti-inflammatory drugs (NSAIDs), azoles (e.g., fluconazole), statins (e.g., pravastatin), anti-TB medication and recreational substances such as alcohol and ecstasy and unproven 'therapies' such as Chinese herbs.

Additionally, NAs and other drugs may impact mitochondrial function (such as metformin or valproate) and so may contribute to liver dysfunction through direct mechanisms. [Abstract 41]

Two presentations looked at hepatic events across multiple studies. [Abstracts 43 and 44] In evaluating hepatotoxicity and mortality events in 21 adult antiretroviral trials, involving 9,003 patients since 1991 investigators for the ACTG used a definition of hepatotoxicity as five fold or greater increases in AST, ALT or bilirubin (Grade 3-4).

Hepatotoxicity events were found in 6.3% of persons on NA alone and 6.2% in persons on triple therapy which included a protease inhibitor (PI) or an nNRTI. Events were more common (7.4%) in individuals on a single NA compared to 4.9% on double NA therapy. Amongst NAs, liver events were more common with ddI (8.7%) relative to AZT (5.5%) or d4T (3.7%). However, these differences were accounted for by studies of high doses of ddI (500-750mg/day) where the grade 3-4 events were seen in 10.3% of individuals compared with only 6.2% on the currently recommended 400mg/day dose.

Comparing PIs and nNRTIs, grade 3-4 liver function events were seen in 5% of PI and 8.2% of nNRTI patients. Presumed drug-related hepatotoxicity deaths were very rare, involving only 0.4% of individuals involved in these clinical trials. [Abstract 43]

Nevirapine Hepatotoxicity

A separate analysis of Nevirapine (nevirapine) trials, including a total of over 2,700 individuals, examined both a database analysis for laboratory changes and investigator reported events. Hepatitis related events were reported in 3.4% of Nevirapine versus 2.2% of control arms, giving an attributable Nevirapine rate of hepatotoxicity of 1.2% in a population of 2,249 of individuals with a median baseline CD4+ cell count of 93/mm3.

In 456 individuals, who were ARV-naïve or had very limited ARV exposure and had a median CD4+ cell count of 363/mm3, the hepatitis and related event rate was 8.1% for Nevirapine and 3.0% for placebo, giving a Nevirapine attributable rate of 5.1% over 1 year. Hepatic events attributable to Nevirapine appeared to be more common in individuals with higher CD4 counts and risk was increased for those with a raised ALT or AST at baseline and co-infection Hepatitis B or C. [Abstract 44]

This creates a degree of dilemma for Nevirapine use: its efficacy appears less good at low CD4+ cell counts but hepatotoxicity is a greater risk in higher CD4 count patients.

In the late breaker session, a Spanish group [Late Breaker Poster 22] evaluated Nevirapine blood levels and risk of hepatic events. They suggest two types of events may be involved in Nevirapine-related hepatotoxicity, one being a hypersensitivity reaction with systemic and/or cutaneous involvement, the second being a delayed hepatic reaction, related to an intrinsic toxic effect of Nevirapine.

Whilst the first reaction may most commonly occur during the first 4 to 6 weeks of Nevirapine therapy, the toxic reaction may occur at any time. Using a case control study design evaluating individuals receiving Nevirapine therapy in triple combination regimens, patients who developed ALT or AST elevation after a mean of 6.1 months from the beginning of HAART had higher median Nevirapine plasma ranges that subjects who did not develop AST elevations (6.25 mg/ml versus 5.2 mg/ml, P=0.025).

In subjects with chronic hepatitis C infection, Nevirapine plasma levels above 6 mg/ml were associated with a 92% risk of liver toxicity. In a multivariate analysis, Nevirapine plasma levels and hepatitis C seropositivity were independent respecters for AST/ALT elevation although the relative risk of hepatic injury was markedly higher with the presence of HCV infection (OR 11.7; 95% CI, 3.2 to 42.8) compared to Nevirapine (OR 1.7; 95% CI, 1.2 to 2.6)).

The difficulty with these data is knowing the cause and the effect: Were Nevirapine levels high because of the hepatitis C or as a consequence of the toxicity rather than specifically causative of the adverse events?

Hepatic and Pancreatic Disease

Another study evaluated hospitalisation for hepatic or pancreatic disease in ARV therapy users from the records of a US health insurer. Evaluation was made of 2,793 individuals contributing 41,304 person months of observation. 15 hepatic and 17 pancreatic hospitalisations occurred over that time, yielding event rates of 3.6 and 3.1 hospitalisations for 10,000 person months of therapy.

The authors found that exposure to ARV therapy was not specifically associated with hepatic- or pancreatic-related admissions, with no difference observed between the different ARV classes. Risk factors for hepatic admissions to the hospital included viral hepatitis and prior hospitalisation for an HIV-related event. As for pancreatic-related admissions, associations included a past history of pancreatic disease and past history for HIV-related disease or use of hepato-toxic illegal substances. [Abstract 542]

Hepatitis B and Hepatitis C Co-infection

Looking specifically at Hepatitis B virus (HBV) co-infection, a single-centre study of 500 individuals in Madrid evaluated elevations in transaminases in individuals under care. They evaluated 500 consecutive patients over the year 2000, of which 56 individuals were hepatitis B surface antigen (HbsAg) positive, including 10 individuals co-infected with delta virus, 10 with hepatitis C virus (HCV), and 9 with both in addition to HBV. 18 individuals developed sudden elevations in transaminase levels during the year of follow-up.

Investigator-assessed mechanisms included immune restoration syndrome, clearance of hepatitis B e antigen (HBeAg) whilst receiving lamivudine, re-appearance of HBeAg positivity, drug-related hepatotoxicity, seroconversion to hepatitis B surface antibody (HBsAb) positivity whilst receiving lamivudine, alcohol abuse or use of other non-antiretroviral hepatotoxic drugs, development of lamivudine resistance and re-establishment of symptomatic acute Hepatitis B in individuals who previously had hepatitis B core antibody (HBcAb) positive HBV DNA (observed only in severely immuno-deficient subjects. [Abstract 552]

The authors concluded that a range of mechanisms may be associated with transaminitis in individuals with HBV co-infection and they added further fuel to the discussion about whether lamivudine monotherapy should be considered in individuals with known HBV as, whilst it may in some cases be associated with sero-conversion or improved serological status, it may also be associated with a transaminase flare associated both with this sero-conversion event and with the development of lamivudine resistance.

This is particularly relevant in the light of the potential widespread availability of other drugs such as tenofovir and adefovir for use in combination antiretroviral therapy to treat HBV in persons with HIV infection.

This group went on to provide a retrospective analysis [abstract 558] of individuals commencing antiretroviral therapy between January 1997 and January 2000 who developed transaminitis (>5-fold rise about the upper limits of normal or 3.5-fold rise above baseline values in those individuals commencing therapy with abnormal transaminases). Of 222 individuals, 38% were infected with HCV, 5% HBV and 2% delta-virus. Significant transaminitis occurred in 21 (9%) of individuals, 10% were receiving PIs, 9% were receiving nNRTIs and 9% were receiving PI plus nNRTI based regimens.

In univariate and multi-variate analyses, alcohol abuse, HCV co-infection and older age were independent significant risk factors. Either PIs or nNRTIs as drug classes or individual drugs within these classes were associated with increased risk of transaminitis.

Bone Diseases

The conference included very limited new information regarding concerns of bone-mineral density in persons with HIV infection, although Pablo Tebas provided a plenary overview of this problem. Although available data are conflicting, Dr. Tebas felt that available evidence supports a role for drug therapy in contributing to loss of bone mineral density in individuals.

Markers of both new bone formation and bone destruction are raised in persons on therapy implying increased bone turnover. He commented that the association with PI use remains speculative. Available evidence suggests no link with testosterone levels and that vitamin D (and its active metabolites) levels are also normal. He pointed to recent published data that found a correlation between osteopenia and osteoporosis and elevated lactate levels.

This may simply be a statistical association (rather than causative association) based on the evaluation of individuals on therapy, but also suggests an alternative hypothesis that there is a link between NA mitochondrial toxicity leading to elevations of lactate and declines in bone mineral density. As Dr. Tebas commented, given the cross-sectional nature of these studies, it is not possible to attribute cause and effect regarding these factors.

The limits of cross sectional studies are such that they cannot separate disease versus drug effects. He underlined that there are many other factors known to be associated with bone mineral density changes in adults both outside of and within the HIV

setting, which include low body mass, which may be secondary to wasting or poor nutrition, past cortico-steroid usage, hormonal deficiencies and the potential for contribution from HIV-related immune system activation and the process of immune reconstitution. In addition to this there are associations in the non-HIV infected population with high blood lipids and low bone mineral density, and therefore metabolic disturbances with HIV infection may be contributory.

He commented that despite the relatively high frequency of osteopenia in cross-sectional surveys, there have been relatively few reported events of bone complications such as fracture. The exception to this appears to be avascular necrosis of the hip although it is unclear whether this is related to loss of bone mineral density or to other vascular problems in individuals with HIV or indeed the classic risk factor of corticosteroid use. He proposed that the management of HIV-related bone mineral density problems is similar to those used in sero-negative individuals, such as the use of nutritional supplements, calcium, vitamin D, exercise, appropriate hormone replacement and the use of therapies such as bisphosphonates. [Abstract 91]

Data from a prospective comparative trial in Spain [Late Breaker Poster 13] looked at bone mineral density in 244 individuals, 146 of whom had been treated for more than 6 months, 56 for less than 6 months and 39 drug-naïve individuals. Assessments using DEXA scan of the lumbar spine, total and neck of femur bone mineral density were assessed at baseline and every 24 weeks.

Over the course of the study, 148 patients (60%) presented with a decline of bone mineral density with 10% achieving a diagnosis of osteoporosis. Duration of HIV infection appeared to be a significant risk factor. Although 5% of individuals who never received antiretroviral therapy had bone mineral densities consistent with osteoporosis, in the treatment groups, the rates of osteoporosis were 11% and 10%.

Whilst this suggests a role for therapy it may also be that those individuals who received therapy were sicker and so more at risk of bone mineral density abnormalities. No differences were detected between the risk of osteopenia or osteoporosis in the use of nNRTI or PI between the regimen.

Hyperlactatemia

Several cross-sectional studies dealt with raised random venous lactate levels. The largest cross-sectional study looked at 1,239 individuals who had been receiving ARV therapy for at least 4 months and an additional 253 individuals who had never received ARV therapy.

Of the 1,239 who had at least one lactate sample, 8.7% had a serum lactate level greater than or equal to 2.5 mmol/L with 9 (0.8%) of individuals above 5 mmol/L, a level considered severe. The problem was observed in similar frequency with male and female patients and duration of therapy was similar between those individuals with normal and raised lactate values. Overall the median lactate levels for the population of 1,239 treated patients was 1.4 mmol/L and amongst the untreated individuals was 1.1 mmol/L. 5 untreated individuals had lactate values above 2.5 mmol/L on a single occasion with one individual having elevated lactate on 2 consecutive occasions (in both cases less than 3 mmol/L).

Associations with hyperlactatemia and therapy use [Abstract 518] and biochemical abnormalities [Abstract 519] were presented. Regarding the whole population, regimens containing didanosine appeared to have an increased relative hazard of a raised lactate whereas those regimens that contained abacavir appeared to have a significantly diminished relative hazard of hyperlactatemia.

Rates of hyperlactataemia where highest in individuals receiving the combination of stavudine and didanosine and the relative hazard was significantly lower in individuals receiving the combination of abacavir plus lamivudine or stavudine plus lamivudine. These data suggest that stavudine is not a key agent in triggering lactate elevation. No significant differences between the relative hazard of hyperlactataemia on stavudine plus didanosine were observed with combinations of zidovudine plus didanosine or zidovudine plus lamivudine.

Additionally, associations with biochemical parameters were observed with hyperlactataemia. In a multivariate model, hyperlactataemia was associated with higher ALT levels and higher glucose levels although the median values were not outside of the normal range. Additionally, hyperlactataemia was associated with a wider anion gap. Individuals with an anion gap of 12-18 had a 4.9-fold greater chance of hyperlactataemia than those with an anion gap of less than 12.

Furthermore, individuals with an anion gap of greater than 18 had an 8-fold higher chance of having an elevated lactate value than those individuals with an anion gap of less than 12. These data raise the possibility that, at least for some individuals, elevated lactates may be a reflection of a shift in acid base homeostasis. However, only 5 events of lactic acidosis were reported in this population.

A second analysis looked only at individuals on first-line therapy. This population of 312 individuals was similar to the overall population studied. For individual NAs, median lactate values in this group ranged from 0.95 mmol/L in individuals receiving zalcitabine to 1.6 mmol/L in individuals receiving didanosine. 25 events of raised lactate were observed in these first line therapy patients with events being more commonly observed in didanosine-based regimens (15.5%) relative to lamivudine-based regimens (5.7%).

Event rates for zidovudine and stavudine did not differ (8% and 9.7%, respectively). In univariate analyses no NA, NA

combination, demographic, or disease factor was associated with a significant risk of raised lactate.

These data are somewhat contrary to previously reported data that have suggested associations with stavudine use. However, these studies had predominantly evaluated individuals who had received multiple-treatment regimens before their assessment for hyperlactataemia, hence they had confounding factors which may have been difficult to correct.

These data, the largest cohort assessed in this way, suggest that there may have been differences between the choice of didanosine or lamivudine but not between the choice of thymidine analogues for risk of lactate elevation. However it is important to underline from this data that the median lactate values with different combinations all remained within normal limits (less than 2.5 mmol/L) and whilst episodic elevations in lactate were common lactic acidosis remained rare. It is therefore unclear what, if any, are the clinical relevance of these differences.

Diarrhoea Management

Several studies evaluated the impact and management of diarrhoea on individuals with HIV infection using HAART. These studies suggested the use of HAART was associated with a diminished frequency of chronic diarrhoea in patients referred to gastro-intestinal evaluation.

In particular, opportunistic pathogens such as CMV, crytosporidosis, and mycobacterium avium complex tended to be proportionally less common in individuals on HAART evaluated for diarrhoea. [Abstract 524] In patients using nelfinavir, several studies evaluated supplementation with probiotics, fibre or l-glutamine. [Abstracts 535 and 536]

In a tiny randomised study of 20 individuals, intervention with acidophilus, soluble fibre and l-glutamine appeared to reduce the need for loperamide therapy as well as overall diarrhoea frequency. A second double-blind study in 25 subjects also found that glutamine initially improved diarrhoea severity relative to a placebo group. The dose of glutamine used in this study was 30 grams thrice daily over a ten day period and thus reflects a considerable treatment burden to manage a problem which may best be resolved by modifying therapy.

References: Unless otherwise noted, all abstract references in the text are to the 1st International IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires, Argentina.

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ANTIRETROVIRALS

Durable HIV Treatment Benefit Despite Low-Level Viraemia: Reassessing Definitions of Success or Failure

Steven G. Deeks, MD for JAMA

Left untreated, human immunodeficiency virus (HIV) replicates at a rapid rate, with the eventual production of billions of new virus particles per day. Given the propensity of HIV to mutate, the possibility exists that each newly produced virus contains at least 1 new mutation. Thus, from a darwinian perspective, ongoing viral replication in the presence of therapy should result in the rapid selection of drug resistance mutations and subsequent virologic rebound.

These basic principles have provided the theoretical context for the “hit hard” therapeutic approach to HIV disease.1 According to current treatment guidelines,1-3 complete viral suppression should be the goal of therapy. Once therapy is initiated, plasma viraemia, as measured by the concentration of viral RNA in plasma, should decrease to below the level of detection using the most sensitive assay available.2, 3 Persistent viraemia suggests ongoing viral replication and treatment failure. The findings from 2 articles in this issue of JAMA raise questions about this conceptual framework, and based on data from the 2 studies, it may be argued that “complete” viral suppression may not be a prerequisite for durable treatment benefit.

Hermankova and colleagues4 present studies involving patients who had achieved and maintained an undetectable plasma HIV RNA level (<50 copies/mL). Using sensitive techniques to amplify plasma viral RNA, virus was identified in plasma in 10 of 20 patients. Genotypic analysis of the isolated viral RNA revealed no evidence of new drug-associated mutations clearly related to the current regimen. The findings indicate that viral replication (defined by the release of virus into plasma) can be identified in patients apparently responding to combination therapy, but that this level of replication appears to be insufficient to select for drug resistance.

Havlir and colleagues5 addressed a similar question in a completely different manner. Patients enrolled in a long-term treatment study were identified retrospectively and stratified into 2 groups: those whose plasma HIV RNA levels remained

consistently below the level of detection (<50 copies/mL) and those whose plasma HIV RNA levels were transiently detectable (>50 copies/mL of RNA with a subsequent measured level of <50 copies/mL) and who were categorized as having intermittent viraemia.

Despite evidence of higher levels of viral replication in the latter group (although not uniformly statistically significant), both groups had similar rates of virologic failure. The occurrence of 2 consecutive HIV RNA levels greater than 200 copies/mL was considered virologic failure.

Before discussing the implications of these data, it is critical to assess whether the presence of HIV RNA in plasma signifies ongoing viral replication. Hermankova and colleagues4 suggest low-level viraemia may simply reflect the release of archived virus from long-lived cellular reservoirs into plasma and not necessarily continuous rounds of productive infection. The hypothesis that viral replication is ongoing in patients with low-level viraemia is supported by several independent lines of evidence. First, genetic evolution within viral envelope sequences has been observed in a small number of treated patients with transient viremia.6, 7 Second, unintegrated viral DNA and unspliced viral messenger RNA, both markers of recent cellular infection, are commonly detected in patients even after several years of effective therapy.7-10 Third, drug-specific mutations may emerge in cellular reservoirs of patients with undetectable or low-level plasma viremia.11 Fourth, patients with low-level viraemia often have increasing amounts of replication-competent virus in cellular reservoirs.12 Thus, when viewed as a whole, it appears that viral replication persists in patients with low-level viraemia, and that complete viral suppression is rarely achieved with current therapies.

If antiretroviral therapy is only partially effective at suppressing viral replication, why were drug resistance mutations and virologic failure observed to be uncommon in patients with low-level plasma viremia?4, 5 One reason may relate to the complex interaction between drug resistance and viral replicative capacity (ie, viral “fitness”). As shown in vitro,13, 14 the initial mutations associated with protease inhibitor resistance result in a virus that is unable to replicate efficiently, perhaps as a consequence of impaired protease function. Only with the accumulation of compensatory mutations does a replication-competent, drug-resistant virus emerge. The level of viral replication in patients with low-level plasma viraemia may be insufficient to select for these compensatory mutations.

Another plausible mechanism for the lack of virologic failure in patients with low-level viraemia relates to HIV-specific immunity. Progressive HIV disease is associated with the loss of HIV-specific T-cell immunity, perhaps as a result of the cytopathic effect of HIV on CD4 T cells.15 Complete viral suppression with combination therapy leads to recovery of T-cell function but lack of sufficient antigenic exposure precludes the generation of effective anti-HIV immunity. Theoretically, partial suppression of viral replication to a low but nonzero level results in a level of viraemia sufficient to generate effective anti-HIV immunity but insufficient to deplete HIV-specific CD4 T cells.16

These considerations raise the question of a viral threshold.4, 5 Is there a level of viral replication below which the degree of viral turnover is insufficient to allow for the emergence and establishment of a drug-resistant and replication-competent variant? Or is there a level of viral replication below which HIV-specific CD4 T cells are generated but not depleted? It is interesting in this regard that 1 patient (A57) in the report by Hermankova et al had a high level of viraemia (400-1000 copies/mL) and was the only patient whose virus evolved over time in ways clearly related to the current regimen.4 Thus, it is possible that resistance and treatment failure may emerge only when the degree of viral replication is sufficiently high.

This concept of a viral threshold is more than an academic question, because if such a threshold exists, then the immediate goal of therapy should be to suppress the virus to below this level. Partially suppressive regimens that achieve this goal, are well tolerated, and preserve future options may be preferred to more potent regimens that are not as well tolerated and do not preserve future options.1, 3 Thus, it is possible that using the most potent regimen possible to completely prevent all viral replication may cause more harm than benefit.

How then should patients with low-level plasma viraemia be managed? Is it necessary to revisit the basic principles upon which current therapeutic strategies are based and allow incomplete viral suppression? While it is reasonable to assume that no virus is preferred to a small amount of virus, it needs to be emphasized that the current approach to antiretroviral therapy (complete viral suppression whenever possible) is based largely on theory and current understanding of disease pathogenesis.1-3 New insights into pathogenesis can and should have an immediate impact on how antiretroviral therapy is administered.

Before consideration is given to modifying therapy in patients with low-level viraemia, the patient’s commitment to therapy and level of adherence should be assessed. Intermittent viraemia may simply reflect intermittent nonadherence. Assuming that adherence is not the primary concern, clinicians have 1 of 4 therapeutic options: continue the current regimen with close observation; label the current regimen a failure and switch to a new regimen (“salvage therapy”); add a drug to the current regimen (“intensification”); or stop therapy altogether and reassess the need for therapy at a future date. The optimal approach will likely depend on each patient’s unique situation. The data from Hermankova et al and Havlir et al suggest that careful observation without treatment modification is certainly reasonable. The larger issue still to be addressed concerns circumstances in which careful observation is not a reasonable option for patients continuing therapy despite detectable viraemia.

Despite these intriguing findings, it is worthwhile to consider the limitations of the data from these 2 studies. First, the apparent

lack of virologic failure and drug resistance in patients with low-level viraemia should be considered a preliminary observation. The median follow-up after the first episode of detectable viraemia in AIDS Clinical Trials Group (ACTG) 343 was only 46 weeks.5 A relationship between low-level viraemia and subsequent virologic failure may become apparent with long-term observation. Similarly, much of the data regarding the lack of resistance in patients with low-level viraemia are cross-sectional.4 Without prospective long-term observation, it is not possible to definitively conclude that a virus population, such as that involved in this study, is static.

Second, the current literature largely applies only to patients receiving long-term protease inhibitor therapy. Protease inhibitor-sparing regimens are now popular, particularly for treatment-naive patients.2, 3 Because mutations associated with protease inhibitor resistance may have greater fitness costs than mutations associated with other therapeutic drug classes, it is possible that low-level viraemia with regimens that do not contain a protease inhibitor may be associated with rapid rates of virologic failure.

These limitations notwithstanding, the data from Hermankova et al and Havlir et al deserve careful consideration by clinicians and by those drafting treatment guidelines. It must now be accepted that current therapeutic regimens may not be able to completely suppress viral replication, even when used under optimal conditions. Fortunately, complete viral suppression does not appear to be a prerequisite for durable virologic and presumably, clinical benefit. Thus, categorizing the response to therapy as a dichotomy (undetectable or detectable, completely suppressed or incompletely suppressed, success or failure) may be misleading. Combination therapy is often only partially effective. The question now is how much viral suppression is required to achieve durable virologic, immunologic, and clinical benefit.

Source: Journal of the American Medical Association. Vol. 286 No. 2, July 11, 2001.

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Anticancer Drug 9-Nitrocamptothecin (9NC) Inhibits HIV-1 Replication

The anticancer drug 9-nitrocamptothecin (9NC) inhibits HIV-1 replication in human peripheral blood lymphocytes (PBLs), researchers report in the July issue of the Journal of Medical Virology.

Dr. M. Reza Sadaie, of NovoMed Pharmaceuticals, Germantown, Maryland, and colleagues note that although previous studies have shown that 9NC inhibits HIV-1 replication, "it is of paramount importance to demonstrate that it is capable of

inhibiting HIV-1 replication in human primary lymphocytes."

Accordingly, PBLs from a noninfected donor were infected with HIV-1, and these and noninfected cells were treated with 9NC. The agent inhibited HIV-1 replication, in a dose-dependent manner, by more than 95%. This essentially was the case whether a single-, double-, or triple-dose regimen was employed.

"Minimal" cytotoxicity was seen following application in infected and noninfected cells. Furthermore, the agent induced apoptosis within 24 hours of treatment in infected, but not noninfected, PBLs.

Dr. Sadaie told Reuters Health that 9NC belongs to a class of medication "that interferes with cellular factors regulating viral gene expression, as well as controlling cell cycle progression."

He added that although it remains to be seen whether the once-daily oral dosage used in trials in cancer patients will be applicable to those with HIV infection, 9NC appears able to purge infected cell reservoirs, and thus has "curative potential in both HIV infection and AIDS associated malignancies."

Ref: J Med Virol 2001;64:238-244.

Source: Reuters Health

TREATMENT GUIDELINES

Updated US Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV and HIV and Recommendations for Postexposure Prophylaxis (PEP)

This report [published in the June 29, 2001 MMWR] updates and consolidates all previous US Public Health Service recommendations for the management of health-care personnel (HCP) who have occupational exposure to blood and other body fluids that might contain hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV).

Summary of Recommendations

Recommendations for HBV postexposure management include initiation of the hepatitis B vaccine series to any susceptible, unvaccinated person who sustains an occupational blood or body fluid exposure. Postexposure prophylaxis (PEP) with hepatitis B immune globulin (HBIG) and/or hepatitis B vaccine series should be considered for occupational exposures after evaluation of the hepatitis B surface antigen status of the source and the vaccination and vaccine-response status of the exposed person. Guidance is provided to clinicians and exposed HCP for selecting the appropriate HBV PEP.

Immune globulin and antiviral agents (e.g., interferon with or without ribavirin) are not recommended for PEP of hepatitis C. For HCV postexposure management, the HCV status of the source and the exposed person should be determined, and for HCP exposed to an HCV positive source, follow-up HCV testing should be performed to determine if infection develops.

Recommendations for HIV PEP include a basic 4-week regimen of two drugs (zidovudine [ZDV] and lamivudine [3TC]; 3TC and stavudine [d4T]; or didanosine [ddI] and d4T) for most HIV exposures and an expanded regimen that includes the addition of a third drug for HIV exposures that pose an increased risk for transmission. When the source person's virus is known or suspected to be resistant to one or more of the drugs considered for the PEP regimen, the selection of drugs to which the source person's virus is unlikely to be resistant is recommended.

In addition, this report outlines several special circumstances (e.g., delayed exposure report, unknown source person, pregnancy in the exposed person, resistance of the source virus to antiretroviral agents, or toxicity of the PEP regimen) when consultation with local experts and/or the National Clinicians' Post-Exposure Prophylaxis Hotline ([PEPline] 1-888-448-4911) is advised.

Occupational exposures should be considered urgent medical concerns to ensure timely postexposure management and administration of HBIG, hepatitis B vaccine, and/or HIV PEP.

Introduction

Avoiding occupational blood exposures is the primary way to prevent transmission of hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) in health-care settings (1). However, hepatitis B immunization and postexposure management are integral components of a complete program to prevent infection following bloodborne pathogen exposure and are important elements of workplace safety (2).

The U.S. Public Health Service (PHS) has published previous guidelines for the management of HIV exposures that included

considerations for postexposure prophylaxis (PEP) (3—5). Since publication of the 1998 HIV exposure guidelines (5), several new antiretroviral agents have been approved by the Food and Drug Administration (FDA), and more information is available about the use and safety of HIV PEP (6—11). In addition, questions exist regarding considerations about PEP regimens when the source person's virus is known or suspected to be resistant to one or more of the antiretroviral agents that might be used for PEP. Concern also has arisen about the use of PEP when it is not warranted. Data indicate that some health-care personnel (HCP) take a full course of HIV PEP after exposures that do not confer an HIV transmission risk (10,11).

In September 1999, a meeting of a PHS interagency working group* and expert consultants was convened by CDC. The PHS working group decided to issue updated recommendations for the management of occupational exposure to HIV. In addition, the report was to include recommendations for the management of occupational HBV and HCV exposures so that a single document could comprehensively address the management of occupational exposures to bloodborne pathogens. This report updates and consolidates the previous PHS guidelines and recommendations for occupational HBV, HCV, and HIV exposure management for HCP. Specific practice recommendations for the management of occupational blood borne pathogen exposures are outlined to assist health-care institutions with the implementation of these PHS guidelines (Appendices A and B). As relevant information becomes available, updates of these recommendations will be published.

Recommendations for nonoccupational (e.g., sexual, paediatric, and perinatal) HBV, HCV, and HIV exposures are not addressed in these guidelines and can be found elsewhere (12—15).

Definition of Health-Care Personnel and Exposure

In this report, health-care personnel (HCP) are defined as persons (e.g., employees, students, contractors, attending clinicians, public-safety workers, or volunteers) whose activities involve contact with patients or with blood or other body fluids from patients in a health-care, laboratory, or public-safety setting. The potential exists for blood and body fluid exposure to other workers, and the same principles of exposure management could be applied to other settings.

An exposure that might place HCP at risk for HBV, HCV, or HIV infection is defined as a percutaneous injury (e.g., a needlestick or cut with a sharp object) or contact of mucous membrane or nonintact skin (e.g., exposed skin that is chapped, abraded, or afflicted with dermatitis) with blood, tissue, or other body fluids that are potentially infectious (16,17).

In addition to blood and body fluids containing visible blood, semen and vaginal secretions also are considered potentially infectious. Although semen and vaginal secretions have been implicated in the sexual transmission of HBV, HCV, and HIV, they have not been implicated in occupational transmission from patients to HCP. The following fluids also are considered potentially infectious: cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid. The risk for transmission of HBV, HCV, and HIV infection from these fluids is unknown; the potential risk to HCP from occupational exposures has not been assessed by epidemiologic studies in health-care settings. Faeces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus are not considered potentially infectious unless they contain blood. The risk for transmission of HBV, HCV, and HIV infection from these fluids and materials is extremely low.

Any direct contact (i.e., contact without barrier protection) to concentrated virus in a research laboratory or production facility is considered an exposure that requires clinical evaluation. For human bites, the clinical evaluation must include the possibility that both the person bitten and the person who inflicted the bite were exposed to blood borne pathogens. Transmission of HBV or HIV infection only rarely has been reported by this route (18—20) (CDC, unpublished data, 1998)

View full report in PDF format:

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5011a1.htm

Source: MMWR. June 29, 2001 / 50 (RR11); 1-42.

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Prevention of Opportunistic Infections Guidelines Updated July 2001

July 2001 DRAFT: 2001 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus

"Major changes in the guidelines since 1999 include:

- Higher level ratings have been provided for discontinuing primary prophylaxis for PCP and MAC when CD4+ T lymphocytes have increased to >200 cells/μL and >100 cells/μL, respectively, for 3 months in response to HAART (AI), and a new recommendation to discontinue primary toxoplasma prophylaxis has been provided when the CD4+ T lymphocyte count has increased to >200 cells/μL for 3 months (AI).

- Secondary PCP prophylaxis should be discontinued in patients whose CD4+ counts have increased to >200 cells/μL for 3 months as a consequence of HAART (BII).

- Secondary prophylaxis for disseminated MAC may be discontinued in patients with a sustained (e.g., 6 months) increase in CD4+ count to >100cells/μL in response to HAART if they have completed 12 months of MAC therapy and have no symptoms or signs attributable to MAC (CIII).

- Secondary prophylaxis for toxoplasmosis and cryptococcosis may be discontinued in patients with a sustained increase in CD4+ counts (e.g. >6 months) to >200 cells/μL and greater than >100-200cells/μL respectively, in response to HAART if they have completed their initial therapy and have no symptoms or signs attributable to these pathogens (CIII).

- The importance of screening all HIV-infected individuals for hepatitis C virus (HCV) is emphasized(BIII).

- Additional information about transmission of human herpesvirus 8 infection (HHV-8) is provided.

- New information on drug interactions is provided, especially with regard to rifamycins and antiretroviral drugs.

- Revised recommendations for immunization of HIV exposed/infected adults and children are provided."

ATIS Guidelines page:

http://hivatis.org/trtgdlns.html

Direct link to PDF of document:

http://www.hivatis.org/guidelines/OIGuidelinesJuly2001.pdf

DRUG TOXICITIES AND METABOLIC PROBLEMS

Carnitine for High Triglycerides

Carnitine is an amino acid that is used to help move fatty substances to places inside cells where they can be burnt to release energy. The parts of a cell where this energy release takes place are called mitochondria. Carnitine can also act as an antioxidant and appears to play a role in maintaining the health of nerves and protecting the liver and kidneys from the toxicity of drugs. Carnitine exists in several forms; the two most commonly used are L-carnitine and L-acetyl-carnitine.

A number of studies have found that people with HIV/AIDS may have less-than-normal levels of carnitine. Signs/symptoms of carnitine deficiency include the following:

- Higher-than-normal levels of triglycerides.
- Weak and/or tired muscles.

As some patients can develop high triglyceride (TG) levels in their blood — whether or not they are taking anti-HIV drugs — research teams in Montreal and Rome have found that supplements of this nutrient may be helpful for patients. The Montreal team recently conducted a small study to observe the effect of carnitine supplements on high TG levels in people with HIV.

Study Details Researchers enrolled 16 adult subjects who had the following profile at the start of the study:

- 1 female, 15 male.
- Average age: 43 years.
- All but one were using protease inhibitors.
- Average viral load: 2,500 copies.
- Average CD4+ count: 218 cells.
- Average TG level: 5.67 mmol/L (normal range 0.5 to 2).
- Average cholesterol: 5.6 mmol/L (normal range 2 to 5.2).
- Average glucose: 5.3 mmol/L (normal range 3.6 to 6.1).

Subjects received 3 grams of L-carnitine daily for an average of nine months.

Results One month after entering the study TG levels had decreased by an average of 39% — a significant decrease from their pre-study levels. This decrease was maintained throughout the study.

According to the researchers, “near-normal TG levels (3 mmol/Litre or lower)” were seen in 54% of subjects after two months of L-carnitine use, and in 69% of subjects after their last lab test. There were no significant changes in cholesterol or glucose levels during the study.

No serious side effects from L-carnitine were reported and, at a dose of 3 grams/day, L-carnitine appears to be relatively safe. The results of this pilot study will be used to plan a larger more complex trial. Carnitine is sold in North America as the prescription drug Carnitor. L-carnitine and L-acetyl-carnitine are also available from some health food stores, particularly in the United States.

This document was provided by CATIE — Canadian AIDS Treatment Information Exchange. For more information visit CATIE’s Information Network at
http://www.catie.ca

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Does efavirenz cause breast enlargement?

The non-nuke efavirenz, although a useful and convenient part of many HIV treatment regimens has been associated with unusual side effects, particularly those affecting the brain, such as dizziness, intense dreams and hallucinations. Researchers in France and Spain have also reported another unusual side effect of efavirenz - breast enlargement in both men and women.

Reports from France

A team of French doctors reported details on six people with HIV/AIDS aged between 43 and 55 years. The six patients had been treated with protease inhibitor (PI)-containing regimens and had developed lipodystrophy. Between one to six months after these patients switched from their PI-based regimens to regimens based on efavirenz, painful breast enlargement occurred. Each of these patients were using different drug combinations; the only drug that they all used in common when breast enlargement occurred was efavirenz. Technicians tested the blood of the patients for levels of many hormones including the following:

- testosterone - DHEA - oestrogen - progesterone - cortisol - FSH (follicle-stimulating hormone) - LH (lutinizing hormone) - TSH (thyroid-stimulating hormone) - All hormone levels were within the normal range.

Doctors continued treatment with efavirenz. In five of the six cases, breast enlargement stabilized. The remaining patients breasts partly shrunk over time. The doctors note that breast enlargement has occurred in 8% of their patients who use efavirenz.

Reports from Spain

Doctors in Spain recently reported details on three male patients who also developed breast enlargement after using efavirenz. Again, extensive and sophisticated hormonal measurements were done but no abnormalities were detected. The Spanish cases were very similar to the ones from France with one major exception: none of the Spanish patients had lipodystrophy before starting efavirenz.

Breast enlargement and female hormones

Breast enlargement usually occurs when testosterone levels fall and oestrogen levels rise. As hormonal measurements indicated that this did not apparently happen in the case of all the cases reported here, doctors remain puzzled as to why this problem occurred. Perhaps a clue lies in work done by researchers in Turino, Italy. Last year, the Italian researchers found that blood samples from patients who took efavirenz appeared to have unusually high levels of the female hormone estradiol. However, when the researchers performed more sophisticated tests, they found that estradiol levels were in fact normal; it was the presence of efavirenz in the blood samples that had confused the initial test used to measure estradiol. They suspect that this occurred because efavirenz may bind to parts of the test that normally detect estradiol. Thus it is possible that efavirenz may have estradiol-like effects in the human body, fooling it into assuming that this drug is similar to a female hormone and triggering the growth of breast tissue or accumulation of fat in the breasts of some people who take efavirenz.

The reports from France, Spain and Italy underscore the need for long- term monitoring of anti-HIV drugs in general and efavirenz in particular. As well, the manufacturer of efavirenz needs to conduct research into preventing this side effect and other troublesome complications of its drug.

Note: The test used by the Italian researchers which detected falsely high estradiol levels was the AIA 21 made by Tosoh corporation in Tokyo, Japan.

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Fat Malabsorption Common Cause of Diarrhoea in HIV-Infected Patients

Fat malabsorption is a commonly undiagnosed cause of diarrhoea in HIV-infected patients, whether or not they have received highly active antiretroviral therapy (HAART), according to a report published in the June issue of the American Journal of Gastroenterology.

Dr. Michael A. Poles and colleagues from the University of California at Los Angeles assessed the incidence of fat malabsorption in 33 HIV-infected patients who underwent evaluation for diarrhoea between June 1995 and April 1999. Twelve of the patients were receiving HAART and 21 were receiving nucleoside analogues only.

All but three subjects had fat malabsorption, including 10 patients in the HAART group and 20 patients in the non-HAART group, the authors report. Mean stool fat weight was lower in the non-HAART group, but both groups had similar mean stool weights.

"The assumption has been that because HAART reduces the incidence of opportunistic infections there would be a subsequent decrease in diarrhoea," Dr. Poles told Reuters Health. "Unfortunately that doesn't seem to be the case, [because] HAART-treated patients still experience a significant rate of diarrhoea," he said. "Fat malabsorption is probably a significant cause of diarrhoea in these patients, certainly worthy of an attempt at diagnosis and treatment."

Dr. Poles noted that "in general, when we think of a cause for fat malabsorption we usually think of pancreatic disease." However, "the patients in the current study did not seem to have any real evidence of pancreatic disease," he said.

"The cause may be more at the molecular level," Dr. Poles postulated. "Nucleoside analogues, and, to a lesser extent, protease inhibitors may have some effect on the pancreas. Findings from a post-mortem study of HIV-infected patients showed that a fairly large proportion do have some evidence of subclinical disease."

Dr. Poles believes that physicians who see HIV-infected patients with diarrhoea need to first consider fat malabsorption in the differential diagnosis. "At our institution, we do a 24-hour faecal fat assay after a fat challenge," he said. "Once we've found fat malabsorption, we treat the patient with pancreatic enzyme replacement."

Ref: Am J Gastroenterol 2001;96:1831-1837.

Source: Reuters Health

Dietary Supplements Can Help with Nelfinavir-Related Diarrhoea

By Brian Boyle, MD for HIVandhepatitis.com

While overall it remarkably improves both quantity and quality of life, highly active antiretroviral therapy (HAART) frequently involves side effects of some sort. These may be short-lived or persistent. In the case of nelfinavir the most annoying and nagging side effect has been diarrhoea.

Numerous treatments have been proposed for this side effect, and some actually work in some patients; however, despite these interventions many patients on nelfinavir continue to suffer from this side effect and its impact on their quality and enjoyment of life.

A study presented at the 1st IAS Conference evaluated whether dietary changes known to reduce diarrhoea in other conditions benefit patients with nelfinavir-induced diarrhoea. Twenty HIV-infected men on nelfinavir with diarrhoea participated in the 12-week prospective study. Sixteen received dietary supplements and 4 did not. The initial dietary supplements consisted of acidophilus/bifid bacteria (1.2 grams/day) and soluble fibre (11 grams/day), and, if diarrhoea persisted at week 4, 10 grams/day of L-glutamine was added and, if needed, increased up to 30 grams/day. Supplement dosing, tolerance, diarrhoea status and loperamide use were assessed monthly.

Weight, CD4+ T cells and viral load were unchanged in both groups after 12 weeks of dietary supplementation. Diarrhoea completely resolved in 9 of the 16 patients who received supplements, with the number of stools per day and incidence of diarrhoea significantly reduced. The patients in this group who did not obtain full relief with probiotics and fibre alone, still appeared to get some benefit from the supplements, with a significant decline in stools per day after starting L-glutamine and a significant decline in loperamide usage.

In the control group, the number of stools per day significantly increased and the incidence of diarrhoea remained unchanged. The use of loperamide in the control group remained stable. Finally, the dietary supplements were well tolerated and patients who received the dietary supplements felt that they improved their quality of life.

The authors conclude "Probiotics, soluble fibre and [L glutamine] significantly reduce diarrhoea for subjects receiving nelfinavir. Improvement was also seen in subjects who were not controlling diarrhoea with [loperamide] alone. Dietary methods to treat HIV diarrhoea are effective and clinically significant."

This is helpful information, especially for patients who are having significant diarrhoea with nelfinavir but are unsuitable, due to resistance or intolerance, for a switch to another antiretroviral regimen. Similar findings were presented in another abstract presented at the IAS conference, which found that L glutamine supplementation (30 grams daily) alone was helpful in controlling nelfinavir- induced diarrhoea and improving overall quality of life.

References

C Heiser and others. Dietary supplementation with probiotics, soluble fibre and L-glutamine (GLN) reduces diarrhoea in HIV+ men receiving nelfinavir (NFV). Abstract 536. 1st IAS Conference on HIV Pathogenesis and Treatment. July 8-11, 2001. Buenos Aires, Argentina.

F Huffman and M Walgren. L-Glutamine Supplementation Improved Nelfinavir (NFV)-Associated Diarrhoea in HIV-Infected Individuals. Abstract 536. 1st IAS Conference on HIV Pathogenesis and Treatment. July-8-11, 2001. Buenos Aires, Argentina.

http://www.hivandhepatitis.com

HCV Coinfection May Have Role in Changes in Body Composition in HIV Patients

Among some HIV-infected individuals receiving antiretroviral therapy, chronic coinfection with the hepatitis C virus (HCV) appears to be related to changes in insulin resistance, plasma lipid profile and body fat composition, according to a report by French researchers.

In a cross-sectional study, Dr. Michel Duong, from Hopital du Bocage, Dijon, and colleagues studied 29 such patients. All had sustained alanine aminotransferase levels at least twice the normal value, according to the team's report in the July 1st issue of the Journal of Acquired Immune Deficiency Syndromes.

In addition, the researchers studied two control groups: 76 HIV-infected individuals receiving antiretroviral therapy who did not have HCV infection, and 123 untreated HCV-infected patients who did not have HIV infection. Lipoatrophy was more frequent among HIV-HCV patients compared with the two control groups, they found.

The insulin resistance level was similar between coinfected patients and HCV-infected control patients, and it was significantly higher in these two groups than in the HIV-infected control patients. The risk of developing insulin resistance significantly correlated with HCV infection (odds ratio 8.8, $p = 0.003$).

Dr. Duong's team also found significantly lower levels of total cholesterol ($p = 0.01$), LDL cholesterol ($p = 0.009$) and triglycerides ($p = 0.02$) among HIV-HCV infected patients compared with HIV-infected patients. They determined that body mass index, triglyceride level, total cholesterol and peripheral fat wasting were some of the variables independently related to HCV infection.

The authors suggest that although "viral coinfections have never been considered as potentially confounding factors in studies dealing with the role of antiretroviral drugs in the development of metabolic and body fat disturbances," the role that HCV infection plays in these processes needs to be clarified.

Ref: J Acquir Immune Defic Syndr 2001;27:245-250.

Source: Reuters Health

OPPORTUNISTIC ILLNESS

Interferon Shows Some Benefit in Preventing AIDS-Related Opportunistic Infections

Treatment with recombinant human interferon-gamma (rIFN-gamma) tends to reduce the number of opportunistic infections and increase survival in patients with advanced HIV disease.

In a study reported in the June 10th issue of AIDS Research and Human Retroviruses, Dr. Lynn A. Riddell, from Barts and the London NHS Trust, and colleagues randomised 84 patients with advanced HIV disease to received thrice weekly rIFN-gamma treatments or placebo for 48 weeks.

The researchers found that rIFN-gamma-treated patients tended to develop fewer opportunistic infections than placebo-treated patients. The immune therapy was particularly effective in reducing the incidence of Candida, herpes simplex, and cytomegalovirus infections. A nonsignificant improvement in survival was also noted with rIFN-gamma treatment.

While several side effects such as headache, fatigue, and rigors were linked to rIFN-gamma therapy, they were reversible, the investigators state. In addition, the immune therapy did not seem to promote HIV activation.

"IFN-gamma has been shown to protect monocytes from HIV infection, down-regulates CD4 on lymphocytes, potentially reducing infectability, and inhibits HIV replication by inducing a defective particle maturation," the authors point out. "These mechanisms may counteract others that increase HIV replication."

Dr. Riddell's team believes that although the treatment differences failed to reach statistical significance, they do warrant consideration of further rIFN-gamma trials.

Ref: AIDS Res Hum Retroviruses 2001;17:789-797.

Source: Reuters Health

ON THE WEB

1st IAS Conference on HIV Pathogenesis and Treatment online coverage at Medscape

http://hiv.medscape.com/IAS2001

Track 1: Current Patient Management

* New Light Through Old Windows: Fine-tuning the Use of Approved Antiretrovirals, by Graeme Moyle, MD, MBBS * Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics: The Continuing Evolution of Pharmacologic Issues in HIV Disease, by Stephen Becker, MD * Update on Antiretroviral Drug Resistance, by Daniel R. Kuritzkes, MD * Management of HIV-Infected Women and Mother-to-Child HIV Transmission, by Alexandra M. Levine, MD

Track 2: Novel Therapeutic Strategies

* HIV Entry: From Molecular Insights to Specific Inhibitors, by William A. O'Brien MD, MS * Investigational Antiretrovirals in Existing Classes, by Mike Youle, MB BS * Strategies for Immune Reconstitution in HIV Disease, by Ronald T. Mitsuyasu, MD * Insights From Basic Science: Implications for HIV Treatment and Prevention, by Mark A. Wainberg, MD

Track 3: Complications of HIV Disease

* Opportunistic Infections: Still a World-Wide Problem, Even in the HAART Era, by Henry Masur, MD * New Developments in AIDS-Related Hematology and Oncology, by Alexandra M. Levine, MD * Adverse Effects of Antiretroviral Therapy: More Noise, Less Clarity? by William G. Powderly, MD

Full text at:

http://hiv.medscape.com/IAS2001

The aetiology of antiretroviral-associated lipodystrophy remains elusive posing problems for its prevention and treatment

Lipodystrophy syndrome was first described in 1998 occurring in HIV-infected individuals receiving highly active antiretroviral therapy.

Drug & Ther Perspect 17(13):11-15, 2001

Full text at:

http://hiv.medscape.com/40803.rhtml?srcmp=aids-072701

Understanding Common Oral Lesions Associated With HIV

Maintaining a healthy, pain-free mouth poses a challenge for the patient with HIV and the provider.

Clinician Reviews 11(6):96-106, 2001.

Full text at:

http://hiv.medscape.com/40922.rhtml?srcmp=aids-072701

Providing Patient Access to Experimental Drugs Through "Compassionate Use," Expanded Access and Accelerated Approval: The FDA Perspective

Introduction, Background, Recent FDA Activities on Access, Industry Concerns About Treatment use of Investigational Drugs, Current Access Procedures, Clinical Trials, Access to a Clinical Trial, Protocol Exception/Exemptions, Access to Investigational New Products, Single Patient INDs, FDA's role in the process, Progress Since FDAMA, Expediting Development, Review, and Approval of New Products, The Office of Special Health Issues, Conclusion.

Following is the statement by Robert J. Temple, MD, on FDA policies regarding "compassionate" or "treatment use" of investigational drugs, made on June 20, 2001, before the Committee on Government Reform, US House of Representatives. Dr Temple is associate director for the Center for Drug Evaluation and Research (CDER) at the US Food and Drug Administration (FDA).

In his testimony before the House Committee, Dr. Temple clarifies several misconceptions about the widely-used term "compassionate use," and reviews the circumstances under which the FDA supports "treatment uses," including "expanded access" and "accelerated approval" of drugs for people with serious illnesses when there is no effective treatment available.

Full text at:

http://www.hivandhepatitis.com/health/071801.html

AIDS Research Today: 20 Views

Twenty commentaries on the current status of AIDS research, by "researchers, clinicians, and community members from varying disciplines, experience and backgrounds" appear in the Summer 2001 issue of CRIA Update, published by the Community Research Initiative on AIDS. These brief summaries offer diverse and informed views of what is happening today in AIDS research — and what may happen over the next several years.
Guy Pujol, Kathryn Anastos MD, Craig Wilson MD, Anna Forbes MS, Denise Goodman, Jay A. Levy MD, Alessandro Di Rocco MD, Tim Horn, Sean R. Hosein, Paul Volberding, MD, Yvette Delph, Roy Gulick MD, MPH, Claire Rappoport MA, Paul Simmons, Julie Davids, Jack Killen MD, Jill Cadman, Donna Tinnerello MS, RD, CD/N, John S. James

Taking the Pulse of AIDS Research

The Summer 2001 issue of CRIA Update takes a look at the direction of AIDS research - where we've been, where we are and where we're going. We've invited a diverse group of researchers, clinicians and community members from varying disciplines, experience and backgrounds to offer their perspectives on the current state of AIDS research. Our goal was to create a mosaic of commentaries, to raise provocative questions and entice our readers to think critically about HIV research and the role we all play in setting the agenda.

We asked people to identify what are, in their opinion, the most important areas of research now underway, where the holes in research lie, what important areas of study are languishing and deserving of more attention, what questions are being ignored and what directions research should take in the future. What follows are their (relatively) unedited responses. We deeply appreciate the efforts of the individuals who contributed commentaries for this issue as well as the many others whose time, energy and commitment have been essential to the advances in HIV treatment over the years.

CRIA was originally founded to conduct clinical research based on the immediate needs of the HIV/AIDS community - community in the broad sense of the word. The goal was, and still is, to design research protocols according to those needs. CRIA has grown over the years, particularly with the development of a vibrant treatment education program that complements our work in clinical research. Our commitment to listening to and acting on community concerns remains intact and our mission clear: CRIA is an independent, non-profit community-based organization committed to improving the length and quality of life for people living with HIV/AIDS through clinical research and treatment education.

While our commitment and our mission are clear and unwavering, our research agenda is always changing to meet current needs. We continue to welcome community initiatives and have recently completed two studies that were suggested by members of our community, including one that demonstrated the efficacy of topical aspirin in relieving the pain of HIV peripheral neuropathy. We continue to look for pharmaceutical industry sponsored drug trials that offer possibly important advances to members of our community such as our current study of human growth hormone for HIV-related fat redistribution. The increasing prevalence of lipodystrophy and the potentially disabling consequences of this syndrome prompted our interest in this study. In the same area, we're involved in studies that look at the effect of different combinations of antiretrovirals on carbohydrate metabolism.

The interest of patients on HAART in trying treatment interruptions to reduce the burden of side effects as well as other problems associated with daily HAART led to our working with a pharmaceutical company to develop a protocol that takes another look at Ampligen, this time to see if its use can prolong the periods of treatment interruption by keeping viral loads undetectable longer than without Ampligen.

The use of complementary and alternative therapies is widespread in our community, and their role and advantages deserve examining. We've developed a study that will help us to understand the role of these integrative therapies in the clinical care of people living with HIV. We hope to build on the findings of this initial work and plan to develop clinical programs that will evaluate specific alternative medicine interventions.

When we look at the direction of AIDS research overall, it's important to acknowledge how much progress we have made. As often as it's said, we need to say it again: many people are living longer and better than they did before antiretroviral chemotherapy. AIDS wards in this country are no longer overflowing with dying patients. Great progress has been made. But HIV infection rates are rising again. We have not learned how to prevent infection, either by effectively helping people to change risky behaviours or by developing effective microbicides or vaccines. Many people are learning that they're co-infected with HIV and hepatitis C, developing cirrhosis and dying waiting for liver transplants. And there are severe limitations to currently

available drug regimens. Resistance to antiretroviral drugs is increasing and many of our friends, clients and patients are running out of treatment options. Side effects are also reducing the effectiveness of these wonder drugs. Different people are developing immune system damage at different rates, revealing interesting and important individual characteristics that affect disease progression.

We face urgent health policy challenges as well, including equitable access to drugs and medical care, the advent of managed care and its effects on clinical practices, and the adequacy and distribution of research funds. For complicated reasons, the advances in HIV treatment have yet to benefit huge numbers of people in our inner cities and rural areas. The diminishing rate of private donations to AIDS research is a disturbing sign that much of the public - because of naiveté, wilful ignorance or worse - now views the disease as chronic, manageable and, therefore, less important.

And, while one may take comfort from the tremendous progress that has been made in this country and the western world, the increasingly apparent ravages HIV is inflicting on the developing world are being addressed far too slowly. Without a vaccine, without significant resources being invested now for the provision of treatment and medical care in the developing world, without a tide of western medical professionals making their skills and knowledge available to help care for the sick in Africa and Asia, without a global Marshall plan for HIV and AIDS, we ain't seen nothing yet.

Full text at:

http://www.criany.org/treatment/summerupdate2001.htm

i-Base MEETING ANNOUCEMENT

The Role of Therapeutic Drug Monitoring in Paediatric HIV Care

Thursday October 18th 2pm - 6pm London venue
Following on from our symposium on paediatric HIV care last Autumn, i-Base will be holding a meeting on the role of therapeutic drug monitoring (TDM) in childrens' HIV care.

Chaired by Professor David Back, this meeting will focus on the clinical utility of TDM and will include presentations from paediatricians from clinics in Europe and the US, where these assays are currently integrated into routine care. Presentations and questions look at the rationale for the use of TDM in clinical practice and the practical issues involved in optimising its use in paediatrics.

Invited speakers include: Professor David Back, Dr David Burger, Professor Ronald de Groot and Courtney Fletcher MD.

This meeting is organised in collaboration with The University of Liverpool and The Family Clinic at St Marys Hospital, London.

Please contact the i-Base office on +44 (0) 20 7407 8488 for a copy of the programme and registration form.

Registration for this event is free. All welcome.

i-Base PUBLICATIONS

i-Base Guide to Avoiding and Managing Side Effects

This 36-page guide to side effects is written in non technical language and has been distributed with this August/September issue of HIV Treatment Bulletin. The booklet provides accurate and supportive information about:

- the risk of side effects and other questions that are important for people about to start treatment
- how side effects are recorded and reported
- using TDM to manage side effects
- changing treatment
- developing a good relationship with your doctor

The guide also includes separate sections on symptoms, reporting and

treatments for the most common side effects.

General side effects covered are:

Diarrhoea; Nausea and Vomiting; Fatigue; Skin Rash; Skin, Hair and Nail Problems; Sexual Dysfunction; Insomnia and CNS side effects.

Systemic side effects covered are:

Peripheral Neuropathy; Liver Toxicity, Rash and Nevirapine; Lactic Acidosis, Pancreatitis and Fatty Liver; Abacavir Hypersensitivity; Indinavir-related Kidney Stones, Lipodystrophy and Bone Mineral Changes.

As with all publications from HIV i-Base, these guides are available free of charge including bulk orders for use in hospitals and clinics.

Please call 020 7407 8488 or use the order form on the back cover to order free copies of this and other i-Base publications.

It is also available to download in pdf format from:

http://www.i-Base.org.uk/pdf/side-effects_aug01.pdf

HIV i-Base

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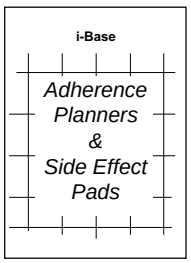

*NEW Guide To Avoiding and Managing Side Effects *(August 2001 edition)*
1 ☐ 5 ☐ 10 ☐ 25 ☐ 50 ☐ 100 ☐ Other_____

Introduction to Combination Therapy *(April 2001 edition)*
1 ☐ 5 ☐ 10 ☐ 25 ☐ 50 ☐ 100 ☐ Other_____

*NEW Changing Treatment - Guide to Second-line and Salvage Therapy *(June 2001 edition)*
1 ☐ 5 ☐ 10 ☐ 25 ☐ 50 ☐ 100 ☐ Other_____

Positive Treatment News (PTN) *from Summer 2001*
1 ☐ 5 ☐ 10 ☐ 25 ☐ 50 ☐ 100 ☐ Other_____

Paediatric HIV Care - March 2001 - Report from i-Base Paediatric Meeting
1 ☐ 5 ☐ 10 ☐ Other_____

*NEW **Introduction aux multithérapies** - French Guide to Combination Therapy
1 ☐ 5 ☐ 10 ☐ Other_____

Introducuzione alla terapia combinata - Italian Guide to Combination Therapy
1 ☐ 5 ☐ 10 ☐ Other_____

Introducción a las terapias combinadas - Spanish Guide to Combination Therapy
1 ☐ 5 ☐ 10 ☐ Other_____

*NEW **Adherence planners and side effect diary sheets** - In pads of 50 sheets - for adherence support
1 ☐ 5 ☐ 10 ☐ Other_____

Please fax this form back or email a request to HIV i-Base:

020 7407 8489 (fax) admin@i-Base.org.uk