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THE THIRD INTERNATIONAL WORKSHOP ON ADVERSE DRUG REACTIONS AND LIPODYSTROPHY IN HIV

ATHENS, 23-26 OCTOBER 2001

Simon Collins, HIV i-Base

While some new insights were presented at this international workshop, there were fewer studies that will have an immediate impact on clinical practice. This may be because lipodystrophy is now an established area of research within mainstream HIV conferences. In contrast to previous meetings there were less than a handful of switching studies, with most interventions focusing on lipid lowering agents developed and researched for other disease areas. However it was interesting to see in vitro studies from last year leading to in vivo studies reported at this years meeting.

Insight into future understanding of risk factors for disease and side effects was shown in the first oral presentation on molecular insights into control of human fat mass and distribution by Stephen O'Rehilly. PPAR receptors are proteins that are important for lipid metabolism, and a case of hereditary insulin resistance with a predisposition to hypertension was shown to be linked to single mutations in the genetic structure of PPAR. It was noted that this example of congenital lipodystrophy - where there is either reduced or absent adipose tissue - was related to the protein rather than lipid building gene.

Insulin resistance

The role of insulin resistance dominated the first of the basic science sessions looking to identify the underlying mechanisms for lipodystrophy and metabolic changes. Protease inhibitors have previously been shown to cause insulin resistance and at last year's meeting a study in HIV-negative individuals receiving indinavir showed a decrease of insulin-stimulated glucose disposal.

Murata and colleagues from Washington University in St Louis hypothesised that direct inhibition of the transport activity of the glucose responsive transporter GLUT-4 contributes to the insulin resistance seen in HIV-positive people on PI therapy. [1] They found that indinavir inhibited insulin-stimulated glucose uptake in 3T3-L1 adipocytes and that this was acute and reversible. Further research from this group was presented by Paul Hruz showing acute and reversible changes in whole body homeostasis in rats that again supported the contribution of GLUT-4 inhibition to the development of insulin resistance.

Noor and colleagues from UCSF showed evidence of the acute effect of indinavir on glucose disposal in vivo. [2] The proposed mechanism for this was again that PIs acutely block the GLUT-4 transporter. This study therefore looked at whether a single therapeutic dose of indinavir would decrease insulin-stimulated glucose disposal without affecting other aspects of insulin action.

Six individuals were studied twice within a 7-10 day period, once with 1200mg indinavir and once with placebo during a 180-minute euglycemic hyperinsulinemic clamp. Comparable insulin and glucose concentrations were reached during the clamp period. However, the rate of glucose infusion required to maintain euglycemia was significantly lower on indinavir ($P<0.05$) compared to placebo. The glucose disposal rate per unit of insulin (m/l) also decreased significantly on indinavir (14.1 ±1.2 to 9.2±0. mg/kg/min, $P<0.001$).

Although these studies specifically focused on indinavir, researchers see this as a class rather than drug specific effect – the greater solubility of indinavir making it an easier compound to investigate.

Behrens and colleagues from Hanover Medical School used positron-emission tomography (PET) to identify defects of muscle uptake in 6 HIV-positive patients on HAART to 6 patients who were treatment naïve, finding whole body glucose was significantly reduced in patients on HAART (1.4±0.38mg/kg/min) compared to untreated patients (4.07 ±0.90 mg/kg/min; $p=0.025$). [3]

Medical interventions

Caron and colleagues from Paris looked for a preventative impact of the insulin sensitising drug rosiglitazone that augments the activity of PPAR-gamma. [4] This group looked at the action and impact of protease inhibitors on adipogenesis and the response to insulin and apoptosis in 3T3-F442A adipocytes and found adipocyte differentiation to be decreasing in rank order for indinavir, nelfinavir and amprenavir respectively. Rosizlitazone was found to prevent this PI effect on cell differentiation and was suggested as a therapeutic possibility.

Elevated levels of free fatty acid (FFA) associated with lipodystrophy were hypothesised by Grinspoon and colleagues as being responsible for insulin resistance. This group reported improved insulin sensitivity following administration of 1000mg acipimox, a powerful lipolysis inhibitor, in two divided doses. This was a randomised controlled placebo study in seven HIV-positive men with lipodystrophy and hyperinsulineamia. Frequently sampled intravenous glucose tolerance tests were performed twice for each patient (separated by 3-7 days) and acipimox or placebo was given in a double-blinded randomised order.

Baseline characteristics:

Age	45±2 years
BMI	28.8±1.9kg/m2
Waist-to-Hips ratio	0.99±0.01
Duration HIV	8±1 year
PI use	4±0.4 years
Insulin sensitivity	0.88±0.3 x 10-4 per uU/ml/min (normal =7.56 10-4 uU/ml/min)

Results:

	Acipimox	Placebo	
FFA AUC	73±8	122±12 mmol/l/270min	*p=0.002*
Insulin sensitivity	1.63±0.5	0.88±0.3 x 10-4 per uU/ml/min	*p=0.015*

Acipimox produced a clear and statistically significant reduction in free fatty acid AUC and increase in insulin sensitivity. The study concluded that strategies to reduce FFA concentrations might be appropriate as a treatment for people with metabolic disturbances and lipodystrophy.

Thyroid function abnormalities

E Billaud and colleagues from Nantes, France, reported on the prevalence of lipid abnormalities in 162 men and 59 women, mainly on HAART regimens in an 18-month cross sectional study between December 1999 and June 2001. [6] Thyroid abnormalities have previously been reported in HIV and eight cases of hypothyroidism were reported by the same team at last year's ICAAC and this study looked into links with lipodystrophy and lipid levels.

Hypothyroidism was defined as thyrotropin levels greater than 4 IU/l and free thyroxine below 8.5 pmol/l. Sub clinical hypothyroidism was defined as isolated elevation of thyrotropin that is asymptomatic and transient hypothyroidism as low free thyroxine not persisting after control.

At the time of the study 84% people were using NRTIs, 34% were using PI and 41% PIs in their combination. 20 people (9%) were treatment naive. Mean age was 40.5 years, mean CD4 count was 457 cells/mm3 and mean viral load was 3 log10 copies/ml.

29 patients (13%) were found to have thyroid abnormalities. There were 12 cases of hyperthyroidism (Grave's disease) 13 people had free T4 below normal. Nine had TSH levels >4 UI/ml upper normal limit.

	Normal range	Mean	Range
Thyrotropin	0.2-4 UI/ml	2.29	0.02-54.7
Free thyroxine	8.5-18 pg/ml	10.73	0.7-21.7
Cholesterol	1.4-2.2 g/l	2,26	0.65-16.4
Triglycerides	0.4-1.6 g/l	3.13	0.3-13.5
HDL Chol	0.4-0.66 g/l	0.47	0.1-1.9
LDL Chol	1.11-1.88 g/l	1.26	0.32-2.73
Glycaemia	0.7-1 g/l	0.90	0.55-1.64
Haemoglobin	12-17.5 g/dl	14.2	8.6-18.6

After control one month later 18 people (13 men, 5 women) had a confirmed diagnosis of hypothyroidism. About 30% of this group had physician diagnosed lipodystrophy.

Compared to Framingham Study, hypothyroidism in the general population is 0.1% in men and 1.0% in women. This study showed levels in HIV population of 7.9% and 8.6% respectively and is obviously a concern that deserves closer monitoring and study.

A poster presentation from Toma also highlighted a high rate of thyroid dysfunction in a prospective 18-month Canadian study of 65 men and 15 women at Hotel-Dieu du CHUM, Montreal. [7]

The following thyroid tests were performed with routine blood tests: antithyroblobulin, anti-thyroid peroxidase antibodies, thyroblobulin, serum thyrotropin (TSH), serum-free thyroxine (T4), triiodothyronine (T3).

Abnormal test results were present in 35% of patients (20 men and 8 women) and although this suggested a higher incidence in women statistical analysis by gender was not included in the abstract.

The following results were recorded:

Anti-thyroid autoantibodies	20
Abnormal high serum thyrotropin (TSH)	5
Abnormal low serum thyrotropin (TSH)	4
Decreased serum-free thyroxine (T4)	7
Decreased serum free triiodothyronine (T3)	6

This resulted in the following clinical diagnoses:

Autoimmune thyroiditis	11 (9 transient)
Hypothyroidism	4 (1 severe)
Euthyroid-sick syndrome	4
Mild primary hyperthyroidism	2

The most frequently associated metabolic complications included cases of hypertriglyceridemia (19), elevated C-peptide (16), lactic acid (5) and abnormal retinol binding (15)

C O M M E N T

Incidence of thyroid disorders in the general population is relatively common, particularly among women over 40, but increased sensitivity of tests (ie TSH) now allow for pre-symptomatic diagnosis and treatment.

These studies in HIV-positive people were small and did not include comparative data to the general population, but they raise a previously unrecognised area to consider given the overlap of symptoms (particularly fatigue and depression) with other HIV-related complaints.

Symptoms of hypothyroidism include increased sensitivity to cold, constipation, pale or dry skin, elevated blood cholesterol levels and unexplained weight (fluid) gain, heavier than normal menstrual periods and depression.

Lipodystrophy and metabolic changes in children

Some studies addressed prevalence of lipodystrophy in children indicating that this presents a similar concern to that of adults.

Vigano and colleagues from University of Milan looked at lipodystrophy in 34 HIV-positive children on HAART, using DEXA for regional body composition (n=34) and MRI for intra-abdominal tissue (n=16). [8] Six of the HIV-positive children were identified as having lipodystrophy symptoms (LD+) at the start of the study and an HIV-negative control group was used for comparison.

The LD+ and LD- children were matched for previous exposure to AZT, d4T and ddI, months on HAART (d4T/3TC plus single PI), CD4 count and plasma RNA <50 copies.

Within the HIV+ group, LD+ children showed higher trunk fat/total fat ratio (p=0.04) and lower limb fat/total fat ratio (P=0.009) and larger intra-abdominal tissue (P<0.0003) than LD-negative children. However, there was a significant difference in fat mass and distribution between HIV-positive children as a whole and the control group, although lean mass was similar. Reduced fat quantity and percentage, lower truncal fat mass and markedly reduced limbs fat mass being reported in both the LD+ and LD- groups compared to controls. This highlighted the importance of careful monitoring, and the current underdiagnosis of sub-clinical lipodystrophy that was found in all children on HAART.

The discussion following this presentation highlighted the importance of careful monitoring and that baseline and subsequent DEXA for lipodystrophy in all children treated with HAART is integrated into the clinical care programmes lead by these clinicians.

Bone studies at lipodystrophy workshop

Several sessions at the meeting looked at complications related to bone, reporting higher rates in HIV-positive people than in age/sex matched general population. The diversity of these changes, links to lipodystrophy and relationship to specific treatments will undoubtedly remain a growing concern; role of gender, exercise and diet should become integrated into future studies. Treatment for bone disorders was not covered at the meeting.

Mondy and colleagues reported on a range of bone histomorphometry identified from needle biopsies and biochemical markers of bone metabolism from nine HIV-positive men with evidence of primary osteopenia. [9]

Four patterns of changes were identified from the biopsy:

- Osteomalacia characterised by greatly increased osteoid volume (OV/BV), thickness (O Th) and surface area (OS/BS), increased mineralised lag time and diffuse irregular tetracycline labelling. Serum bone alkaline phosphotase and osteocalcin were also increased. (n=1)
- High bone turnover osteoporosis, characterised by increased osteoid volume, surface area and osteoblast content, increased bone turnover (increased mineralisation, formation and tetracycline labelling at all osteoid/mineralised bone interfaces. Alkaline phosphotase was moderately increased. (n=1)
- Inactive osteoporosis, characterised by low osteoblasts and osteoclasts, decreased volume, thickness, surface area, bone formation rate and mineralising surface. (n=2)
- Osteoporosis with normal remodelling, relatively normal tetracycline labelling and indices of bone turnover.

The diversity of the forms of osteoporosis may imply different mechanisms behind the pathogenesis of bone changes in HIV-infection. The small numbers in the study did not show any correlation between ARV therapy and pattern of osteoporosis.

Rozenbaum and colleagues from Paris, looked at rates of osteoporosis and osteopenia in HIV-positive men (age 25-55) treated with PI (n=47), NNRTI (n=23) or triple nucleoside(n=23) therapy for >18month, together with a group of untreated patients (n=25). BMD was measured by DEXA at femoral neck, trochanter and lumbar spine. [10]

Results identified frequency of osteoporosis at 7-11% and osteopenia at 45-55% in the group as a whole, with no difference being reported (so presumably wasn't detected) by treatment regimen. Lipodystrophy was present in 89% of PI-treated and 74% of non-PI treatments compared to 4% of untreated group.

Falutz and colleagues from Quebec used DEXA scans to look at whether total body weight, fat mass (FM) and lean body mass (LBM) exerted an independent influence on bone mineral content (BMC) in 27 patients (24 male, 3 female). 15 people had typical features of lipodystrophy (LD). [11]

Trunk/extremity lean body mass was similar in LD+ and LD- patients and trunk/extremity fat mass was higher in the LD+ group. No correlation was found between total fat or lean body mass and bone mineral content in either group. However associations were for the LD+ group between trunk FM and trunk BMC, arm LBM and arm BMC, and leg LBM and leg BMC (p=0.01, 0.02 and 0.005 respectively). No correlations were found for the LD- group other that leg LBM and leg BMC (p=0.04).

Multiple regression analysis showed that FM and weight contributed significantly (23% and 20%) to total body BMC in LD+ patients, and that FM, LBM and height were contributory factors (25%, 23% and 31%) for those who were LD-.

Madeddu and colleagues from Sassari, Italy, reported high rates of osteoporosis and osteopenia when comparing spine bone density (DEXA), serum osteocalcin, bone alkaline phosphatase between 148 HIV-positive patients (98 male, 50 female) to 55 age-sex matched HIV-negative people. Of the HIV-positive group, 85 were on a PI-based combination.

	PI-based	Non-PI or naïve	
Osteoporosis 1	9/85 (22%)	5/63 (8%)	p<0.05
Osteopenia	30/85 (35%)	23/63 (37%)	NS
BMD (mg/cm2)	0.92±1.3	0.97±1.3	p<0.01

*BMD in HIV –ve controls = 0.99±0.1

Osteocalcin was significantly higher and bone alkaline phosphotase significantly lower in HIV-positive groups compared to controls. Additional differences between the PI and non-PI receiving HIV-positive groups included significantly higher osteocalcin, bone alkaline phosphotase, urinary pyridinium cross-links in the PI-receiving group. Bone density and biochemical markers did not correlate with disease severity or treatment time. [12]

Mauss and colleagues from Dusseldorf assessed bone mineral density and metabolism in 24 asymptomatic patients (21 male, 3 female) who had HIV infection >10 years and ARV treatment >5 years and were not treated with corticosteroids or testosterone. [13]

Median characteristics included median age 48 years (33-65), median duration of HIV infection 13 years (10-19) and median time on ARV 6.5 years (5-11). Nearly all patients were multiple nucleoside, PI and NNRTI experienced. 12/24 patients were found to be osteopenic (compared to an expected 4/24 in an age-matched population) although none had osteoporosis. Elevated markers of bone resorption were present in many of the osteopenic patients.

Finally, Lilienfield and colleagues searched 14,000 records from the MediCal (Medicaid California) database for reports of osteoporosis, aseptic osteonecrosis or hip fracture. [14] This BMS sponsored study reassuringly found no statistical difference between d4T and AZT use and the risk of these events (2.3 versus 2.9%, p>0.05) and that from this database at least, the risk is as great using either of these drugs.

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TREATMENT ACCESS

Survey reveals pregnant Zambians support universal nevirapine treatment

Graham McKerrow, HIV i-Base

A majority of pregnant women in Lusaka, Zambia, support the mass treatment of pregnant women with nevirapine, rather than targeted treatment, if it means more positive women will be treated, according to a survey published in the Lancet of 10 November.

Single-dose nevirapine has proven efficacy and cost effectiveness in preventing perinatal transmission of HIV, and manufacturer Boehringer Ingelheim is committed to donating the drug throughout the developing world. The debate is now focusing on how to distribute the drug in poor countries: Lusaka District allocates $5 per patient per year for obstetrical care, report Dr Jeffrey Stringer and colleagues at Lusaka and Alabama, USA.

The researchers say a shortage of resources could mean choosing between the mass distribution of nevirapine to all pregnant women regardless of their HIV status, or HIV testing for only some women and the treatment of those who test positive. Researchers questioned 310 women attending antenatal clinics. The overwhelming majority (74 per cent) only wanted to be treated if they were positive, but given a choice between mass treatment for all pregnant women or testing and treatment of half the women, most (60 per cent) chose universal treatment.

“This survey suggests that most women in Lusaka would support a mass therapy approach if it would allow a greater proportion of women to receive nevirapine. Women’s preferences should be considered as programme policies are developed in Africa and elsewhere,” they write.

Reference: Sinkala M, Stout JP, Vermund SH et al. Zambian women’s attitudes toward mass nevirapine therapy to prevent perinatal transmission of HIV. Lancet 2001 Nov 10;358(9293):1611-2

Full text at:

http://www.thelancet.com/journal/vol358/iss9293/full/llan.358.9293.original_research.18334.1

ANTIRETROVIRALS

Delaying antiretroviral therapy may be considered for many patients

Delaying antiretroviral therapy may not lead to poorer virologic outcomes for many patients with chronic HIV infection, according to a report in The Journal of the American Medical Association for November 28. The investigators report that a low CD4 cell count and a high viral load at baseline were not linked to a poorer virological outcome.

Separate study findings in the same journal issue indicate that only baseline CD4 cell counts are predictive of disease progression to AIDS or death in chronically infected patients who delay antiretroviral therapy.

For patients with asymptomatic HIV who have not received antiretroviral therapy (ART), it is unclear whether such therapy should be initiated immediately or deferred until CD4 cell count is lower, and/or the plasma viral load is higher. Early therapy brings immediate intervention against a virus known to be causing immune damage, provides the potential for preservation of HIV- specific CD4 cells and the micro-architecture of lymphoid organs, and lowers the viral load to reduce infectivity and prevent opportunistic diseases with high fatality rates. Delaying therapy, alternatively, means avoiding the risk of drug toxic effects, selection for drug resistance, and the inconveniences of adhering to a complex regimen for an extended time period.

Successful treatment of HIV requires a profound and prolonged virological response. A key consideration when deciding when to initiate ART is whether the virological response is likely to be compromised by any delay. However, the relationship between baseline CD4 cell count, baseline viral load, and viral load response has not been characterized in detail.

In order to characterize the relationship of viral load response to ART with baseline CD4 cell count and baseline viral load, the authors studied an inception cohort of 3,430 therapy- naïve patients, of whom 3,226 patients had at least 1 viral load count after the initiation of ART. [1] The cohort consisted of patients in the Swiss HIV Cohort Study (SHCS), Frankfurt HIV Clinic Cohort (FHCC), and EuroSIDA studies who initiated ART 1) consisting of at least 3 drugs in combination, 2) after January 1, 1996, 3) with a viral load and CD4 cell count measurement available 6 months before, and 4) when the most recent viral load was greater than 500 copies/ml. For viral load outcomes, the investigation required at least one measurement available after the start of therapy.

All 3 cohorts are clinic-based, capturing in a prospective fashion the ongoing clinical and laboratory marker status of complete populations of clinic patients, and for the EuroSIDA, a consecutive group of clinic attendees over a stipulated time period. For the EuroSIDA and SHCS, viral load and CD4 cell counts were measured approximately every 3 months. In the Frankfurt HIV Clinic Cohort, viral load and CD4 cell counts were measured every 1 to 2 months. For these analyses, the assays were sensitive to a viral load above 500 copies/mL.

Viral response used three measures. One measure was the time to viral load of less than 500 copies/mL. Thirty-two weeks was chosen as a period over which, from previous experience, the viral load would be expected to have declined to below 500 copies/mL. The second measure pertained to only those patients for whom there was at least 1 viral load measure available between weeks 22 and 40 and classified them according to whether the viral load measured closest to week 32 was below 500 copies/mL. The third measure -restricted to those patients who achieved a viral load of less than 500 copies/mL by 32 weeks - was the time from viral load first declining below 500 copies/mL to the time of the first of 2 consecutive values above this level.

The authors report that lower CD4 cell counts and higher viral loads at baseline were not associated with poorer virological outcome of ART. However, those with baseline viral loads of greater than 100,000 copies/mL had a lower rate of achieving viral suppression. “The decision of when to initiate therapy is complicated, and many factors must be taken into account. We have provided information concerning only 1 issue, albeit an important one. Until firm evidence from randomised trials is available, it is pieces of evidence such as this study that clinicians and patients must refer to when deciding on when to initiate therapy,” the author concluded.

In the second report, Dr Julio S. G. Montaner from the University of British Columbia, Vancouver, Canada, and colleagues performed a population-based analysis of 1219 antiretroviral naïve HIV-infected men and women. These patients started a three-drug antiretroviral regimen between 1996 and 1999. [2]

Patients with a baseline CD4 count of fewer than 50/μL were 6.67 times more likely to die compared with patients with baseline CD4 counts of at least 200/μL. Those with baseline CD4 counts of 50/μL to 199/μL were 3.41 times more likely to die than those with baseline CD4 count of at least 200/μL, Dr. Montaner’s group reports.

“Disease progression to AIDS and death clustered among patients starting therapy with CD4 cell counts less than 200/μL in our cohort,” the researchers note. “Rates of disease progression and death were independent of age, sex, prior AIDS diagnosis, protease inhibitor use and plasma HIV RNA levels,” Dr Montaner and colleagues write.

"Based on these studies, several somewhat divergent clinical conclusions could be drawn," Dr. Roger J. Pomerantz from Thomas Jefferson University, Philadelphia, comments in a journal editorial.

"Nevertheless, it seems that a reasonable conclusion would be to focus primarily on CD4 T-lymphocyte count for determining initiation time for antiretroviral therapy in many infected patents," Dr Pomerantz advises.

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Full texts available at:

http://jama.ama-assn.org/issues/v286n20/rfull/joc02184.html

http://jama.ama-assn.org/issues/v286n20/rfull/joc10361.html

Source: Centers for Disease Control & Prevention (CDC), HIV/STD/TB Prevention News Update

Correlation between reduction in plasma HIV-1 RNA concentration 1 week after start of antiretroviral treatment and longer-term efficacy

Levels of concentration of HIV-1 RNA in plasma are standard markers for AIDS and death during the course of the disease, as well as indicators of the efficacy of antiretroviral treatment. Virological responses to treatment are commonly measured by HIV-1 RNA levels 4-12 weeks after the start of treatment. The kinetics of the treatment in the initial stages is not commonly measured.

According to guidelines produced by the Department of Health and Human Services, decisions to change therapy include less than a 0.50-0.75 log reduction in plasma HIV-1 RNA by 4 weeks. However, viral resistance can develop during these weeks if therapy is suboptimal, and patients could be exposed unnecessarily to ineffective and toxic drugs. Therefore, earlier prediction of drug efficacy could be helpful for optimising therapy.

The investigators assumed that the initial slopes of HIV-1 concentration changes during the first week of therapy and is linked to drug efficacy. The authors thus investigated the possibility of using the very early dynamics of HIV-1, assessed by measurement of daily samples for different cohorts of patients, including patients on HAART, as a possible predictor of drug efficacy in the longer-run.

Data were obtained from three cohorts of patients. One consisted of 52 children who had never received protease inhibitors, who completed 12 weeks of a phase I trial of indinavir monotherapy in 1996. The second cohort comprised 34 adults, naïve to protease inhibitors and non-nucleoside reverse transcriptase inhibitors, treated with a four-drug combination regimen during 1997-2000. The third cohort consisted of 38 children, naïve to protease inhibitors, who completed 12 weeks of a phase I trial of ritonavir monotherapy in 1995-1996.

The number of CD4 cells was measured by flow cytometry. HIV- 1 RNA concentrations in plasma were measured by PCR. The baseline HIV-1 RNA concentrations were calculated as an average of two log concentrations from samples taken on day 0 and the previous day or a few days before. The baseline variance was smaller than 0.3 log. Patients with a continuous decline of HIV-1 concentrations and in whom HIV-1 was either undetectable or declined by more than 1.5 log at 12 weeks were defined as good responders; the rest were poor responders.

There was no significant difference in the baseline plasma HIV-1 RNA concentration between groups on monotherapy and on HAART. The mean change in log HIV-1 RNA concentration for poor and good responders was 0.82 and 2.10 log, respectively, at week 5, and 0.50 and 2.60 at week 8. According to the authors, "the individual virus decay rate constants (k) at day 6 correlated significantly ($r>0.66$, $p<0.0001$) with changes in HIV-1 concentrations at 4, 8 and 12 weeks, and correctly predicted 84% of the responses with a cut-off value of $k=0.21$ per day (in log scale). Reduction in plasma HIV-1 less than 0.72 log by day 6 after initiation of therapy predicted poor long-term responses in more than 99% of patients."

The authors took advantage of what are now judged to be suboptimal regimens of ritonavir and indinavir monotherapy that were given several years ago. For patients on single or combination therapy, the earliest and most important indicator of drug efficacy determining long term (12-week) response was the change in plasma HIV-1 RNA levels at days 3-6. This indicates that early measurement will indicate efficacy with HIV-1. However, as the authors indicate, this method may not work with all cohorts, was used with naïve patients, and is dependent upon adherence to treatment, a major problem in current HIV-1 treatments. The authors recommend further prospective studies with larger homogeneous cohorts and cohorts of drug-experience patients.

Ref: Polis MA, Sidorov IA, Yoder C et al. Correlation between reduction in plasma HIV-1 RNA concentration 1 week after start of antiretroviral treatment and longer-term efficacy. Lancet 2001 Nov 24;358(9295):1760-1765.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11734232&dopt=Abstract

Source: Centers for Disease Control & Prevention (CDC), HIV/STD/TB Prevention News Update

One week on, one week off experimental regimen might reduce the cost and toxicities of HIV therapy

A pilot study at the National Institute of Allergy and Infectious Diseases (NIAID) suggests that it may prove feasible for certain people with human immunodeficiency virus (HIV) disease to move from a continuous regimen of anti-HIV therapy to a strategy in which they discontinue and then resume anti-HIV therapy in a pre-planned, cyclic fashion.

This approach is known as "structured intermittent therapy." In the NIAID study, 10 patients received repeated "on-off" cycles of therapy: seven days of treatment with potent combinations of HIV medications, followed by seven days off the drugs. At the time of study enrolment, the patients were being successfully treated with continuous highly active antiretroviral therapy (HAART). For the study, they switched to the intermittent HAART regimen with no apparent deleterious effects on the course of their disease, and with a significant reduction in certain HAART-related side effects.

Because it halves the total time during which patients receive anti-HIV medications, structured intermittent therapy could significantly reduce the costs and side effects of anti-HIV drugs, important issues in both resource-rich and poor countries," notes lead author Mark Dybul, M.D., NIAID assistant director for medical affairs. "It is important to stress, however, that the results of randomised, controlled clinical trials - currently under way - are needed to prove the benefits of this experimental approach before it can be recommended to patients outside the setting of a controlled clinical trial. Don't try this at home!"

The NIAID researchers, led by Dr Dybul and NIAID Director Anthony S. Fauci, M.D., report their findings in the December 4 online early edition of the Proceedings of the National Academy of Sciences. The bulk of the research was conducted within the NIAID Laboratory of Immunoregulation, which Dr Fauci directs and where Dr Dybul is a staff clinician.

The authors note that HAART has provided extraordinary benefits to many people infected with HIV, substantially reducing HIV-related morbidity and mortality. Unfortunately, the utility of HAART is limited by significant short- and long-term toxicities, complicated dosing regimens and associated problems with adherence, and the development of drug resistance. In addition, high monetary costs have precluded the widespread use of HAART in resource-limited countries.

"With further research, we would hope that the approach of structured intermittent therapy for HIV disease will lead to decreased HAART-related toxicities, reduced costs, and, potentially, to improved adherence," says Dr Fauci. "Ultimately, structured intermittent therapy might be adapted for use in developing nations, where more than 95 percent of the world's HIV-infected people live, but where very few have access to HAART because of the cost of antiretroviral agents."

Study details

Upon study entry, patients were receiving HAART daily, in regimens that included combinations of three or four anti-HIV drugs. This therapy had kept patients' HIV levels below 500 copies per millilitre (mL) of plasma for more than six months, and below 50 copies/mL at the time of enrolment. All patients entering the study had CD4+ T-cell counts of at least 300 cells per cubic millimetre (mm3) of blood. CD4+ T cells are crucial immune cells typically depleted during HIV disease.

After enrolment in the NIAID study, the patients received a four-drug regimen comprising stavudine, lamivudine, indinavir and ritonavir, administered twice per day in the intermittent schedule of seven days on therapy followed by seven days off therapy. This on-off cycle was repeated 16 to 34 times - that is, for 32 to 68 weeks.

While receiving seven-day-on, seven-day-off cycles of intermittent HAART, study participants had no significant increases in the amount of HIV in their bodies, as determined by tests that measured HIV in their plasma and lymph nodes, as well as within immune cells. In addition, patients' CD4+ T-cell counts were maintained at pre-study levels, and no evidence suggested the development of resistance to HAART medications.

Importantly, the investigators also noted significant decreases in serum cholesterol and triglyceride levels, which frequently are elevated in HIV-infected individuals receiving HAART and can contribute to heart disease and other problems. Mean serum cholesterol and triglyceride levels dropped 22 percent and 51 percent, respectively, after 24 weeks of intermittent therapy.

"These provocative findings have spurred larger, controlled clinical trials of structured intermittent therapy by our group and others," says Dr Fauci. "Hopefully, data obtained from these larger studies will validate the potentially important findings in the pilot study."

Ref: M Dybul et al. Short cycle structured intermittent treatment of chronic HIV infection with highly active antiretroviral therapy: Effects on virologic, immunologic, and toxicity parameters. Proceedings of the National Academy of Sciences Early Edition online (December 4, 2001).

Copies of the article are now available to reporters from the PNAS news office, tel. (202) 334-2138, or e-mail pnasnews@nas.edu.

C O M M E N T

The obvious caveat in such approaches (as with triple nucleoside regimens) is that they may be applicable only to certain narrow categories of patients. Triple nucleoside regimens demand that patients be treatment naïve for acceptable efficacy, or when switching, that patients have never previously experienced virological failure on nucleoside analogue containing combinations.

Structured intermittent therapy (SIT) in this study required successful suppression on continuous therapy, suppression to less than 50 copies/mL at time of switch to SIT, and CD4 counts greater than 300 cells/mm3. It is unclear from this report if successful virological suppression prior to SIT occurred with the first ever regimen in these patients or if some had experienced varying degrees of virological failure on prior partially suppressive regimens.

It is now becoming increasingly clear that individual histories of HIV-infection and attempts at antiretroviral therapy may be crucial in determining suitability for these experimental protocols.

Enteric coated didanosine significantly reduces nausea, bloating, GI upset

Graham McKerrow, HIV i-Base

Enteric-coated didanosine (Videx EC) significantly reduces nausea, bloating, GI upset, diarrhoea, abdominal cramps and gas, according to a study, using patient symptom scores recorded in diaries.

Didanosine EC capsules, which contain enteric coated beadlets that are absorbed in the small intestine, are better tolerated than the original buffered tablet formulation of the nucleoside transcriptase inhibitor, according to the study.

Dr Laureen Kunches, who led the research said she conducted the study because clinicians and patients needed to know, in real-world conditions, how side effect experiences of the new didanosine EC formulation compared with previously available forms of the drug.

In a six-week open-label trial researchers at Boston-based John Snow Inc Clinical Research evaluated the frequency and magnitude of gastrointestinal side effects in 42 adults with HIV infection before and after they switched to didanosine EC from the buffered form of didanosine. All of them had GI symptoms of at least “moderate severity” while taking the buffered tablet.

“All 42 study subjects preferred the EC form,” the researchers report in the October 1 issue of the Journal of AIDS. Switching to didanosine EC led to significant reductions in nausea, bloating, GI upset, diarrhoea, abdominal cramps and gas, according to the patient symptom diaries.

Dr Kunches said the study leads her to believe that didanosine can now be considered for a wider group of patients, including those who might be sensitive to GI upset or diarrhoea.

People making treatment regimen decisions will not have to be faced with either the substantial GI issues or the unpleasant taste of the original forms of didanosine, Dr Kunches added. These improvements should also improve adherence to treatment and appear to justify the additional price for the EC form, she said.

Ref: Kunches LM, Reinhalter NE, Marquis A et al. Tolerability of enteric-coated didanosine capsules compared with didanosine tablets in adults with HIV infection. Journal of Acquired Immune Deficiency Syndrome 2001 Oct 1;28(2):150-3.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11588508&dopt=Abstract

Secondary mutations in HIV-1 protease predict treatment failure in naive patients

Drug-naive HIV-infected patients with secondary mutations in the protease region of HIV are significantly more likely than HIV-infected patients without these mutations to fail antiretroviral therapy at 24 weeks.

“If confirmed in independent studies, this result may justify the increased use of HIV genotyping in drug-naive patients requiring antiretroviral therapy,” Dr Carlo F. Perno, of the University of Rome Tor Vergata, and colleagues suggest in the October 15th issue of the Journal of Infectious Diseases.

Dr Perno’s group examined the role of mutations in the protease and reverse-transcriptase regions of HIV in predicting virologic failure in 248 drug-naive, HIV-infected patients. All patients had just begun antiretroviral therapy with a multidrug regimen containing two reverse transcriptase inhibitors and at least one protease inhibitor.

Virologic failure at 24 weeks correlated significantly with the number of protease region mutations in each patient. Secondary mutations at two sites in particular, codons 10 and 36, were the strongest predictors of virologic failure. "According to the model estimate, patients with either mutation were at twice the risk of having virologic failure at week 24 than were patients with neither mutation," the team writes. ($p = 0.004$).

And this risk remained even after accounting for other factors known to affect treatment failure, such as CD4 cell count and pretherapy viral load.

Both mutations were common, with mutations at codons 10 and 36 present in 39.3% and 40.0% of patients, respectively. Given this prevalence, Dr Perno and colleagues suggest that the mutations may represent natural polymorphisms in the HIV protease region.

"Further data are needed to confirm whether our results would persist in cohorts of naive patients from different geographic regions, who start therapy at different disease stages and who are infected with HIV subtypes different from those circulating in Italy," the researchers add.

Dr Perno's group concludes that "randomised studies are warranted to assess whether drug-naive patients with selected secondary mutations should be treated with a non-nucleoside reverse-transcriptase inhibitor-containing regimen or with a regimen containing dual protease inhibitors."

Ref: Perno CF, Cozzi-Lepri A, Balotta C et al. Secondary mutations in the protease region of human immunodeficiency virus and virologic failure in drug-naive patients treated with protease inhibitor-based therapy. Journal of Infectious Diseases 2001 Oct 15;184(8):983-91.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11574912&dopt=Abstract

Source: Reuters Health

Antiretroviral regimen complexity, self-reported adherence, and HIV patients' understanding of their regimens: Survey of women in the HER study

Research regarding treatment adherence in chronic diseases, such as hypertension, suggests that increasing complexity in the medication regimen is associated with decreasing patient adherence. However, less is known about the relationship between regimen complexity and adherence in the treatment of HIV/AIDS.

This study confirms recent national reports that simplifying regimens is the most frequent strategy that HIV providers use to enhance their patients' adherence to highly active antiretroviral therapy (HAART). The study examined the relationship between HAART regimen complexity and patient understanding of correct dosing to adherence (missing doses in the past 1 and 3 days).

Using a cross-sectional survey of the multi-centre, longitudinal cohort of the natural history of HIV disease in US women - the HIV Epidemiologic Research Study (HERS) -the authors implemented an instrument designed to survey drug adherence. The HERS adherence survey was administered by trained interviewers as a "one time only" questionnaire to all HIV-infected participants (regardless of medication use) at the visit that occurred between April 1, 1998 and December 31, 1998. Spanish-speaking interviewers administered a Spanish-language version of the survey instrument to participants whose first language was Spanish and who were not fluent in English. A total of 289 HIV-infected women in the HERS cohort completed the adherence survey. In terms of race/ethnicity: 53 percent of patients were black, 25 percent were white, and 17 percent were Latina.

Questions were asked about each medication taken.

For each medication each participant was asked to specify the way in which they were instructed to take the medication, both frequency and instructions about timing of dosing to food intake. Those not taking HAART answered questions about why they were not currently using the medication.

The two primary outcome variables measuring adherence with therapy were patient self-report of whether any antiretroviral medication doses had been skipped the previous day and in the previous three days. "Patient understanding" of the HAART dosing regimen was quantified using a binary outcome, based on whether the patient's self-report of instructions related to taking the medication on an empty stomach and dosing frequency of their medications agreed with the standard prescribing practice. Use of drugs in which standard practice could vary was taken into account, and questions were adjusted to meet that variance.

The analysis consisted of basic summaries of patient characteristics, bivariate summaries of the relationship between dose skipping and various clinical and demographic factors and a logistic regression analysis to characterize the probability of skipping a dose as a function of patient-level variables simultaneously. The clinical and demographic factors included the Center for the Epidemiologic Study of Depression Inventory (CESD) collected on all HERS participants at each study visit.

Many of the patients were depressed; with 46 percent having a CESD score >23. The patients had a wide range of viral loads and CD4 counts immediately before collection of the adherence data. However, more than half had viral loads of <1000 copies/ml.

Nearly two-thirds of the patients (65%) were on a regimen that included three or more antiretrovirals; 64 percent were taking an antiretroviral regimen that contained at least one protease inhibitor. More than 40 percent of patients reported that they were prescribed a regimen that contained at least one medication that had to be taken three or more times daily. Fifteen percent reported that they were taking at least one medication that had to be taken on an empty stomach.

Only 75 percent correctly understood the dosing frequency; 80 percent correctly understood the food- dosing instructions, and 63 percent correctly understood both types of instructions. Many patients had skipped a dose recently; 24 percent had skipped a dose in the past 1 day (yesterday), and 32 percent had skipped a dose in the past 3 days.

The association between missing doses and patient characteristics showed that demographic, clinical and behavioural variables were not significant. Based on self- reported dosing instructions, there was no association between missing a dose and empty stomach instructions or maximum dose frequency.

Predictors of skipping doses were: 1) having a prior CD4 count of greater than 500; this CD4 level was associated with a lower likelihood of skipping doses in the previous 3 days; 2) younger age was also associated with lower likelihood of missing doses in the previous 3 days. According to the authors, "None of the other clinical, behavioural or demographic characteristics, including race/ethnicity, current of past injection drug use, or educational attainment was a significant predictor of missing doses in the previous 3 days in this model."

Ref: Stone VE, Hogan JW, Schuman P et al. Antiretroviral regimen complexity, self-reported adherence, and HIV patients' understanding of their regimens: survey of women in the her study. J Acquir Immune Defic Syndr 2001 Oct 1;28(2):124-31.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11588505&dopt=Abstract

Source: CDC HIV/AIDS, STD, TB Prevention News Update

Study indicates NNRTI mutations have little effect upon HIV-1 replicative capacity

Brian Boyle, MD for HIVandHepatitis.com

During the past 5 years, highly active antiretroviral therapy (HAART) has improved morbidity and mortality rates in HIV-positive patients. In some patients on HAART, these improvements have been observed and CD4+ T cell increases have been maintained, despite the presence of persistent low-grade virologic replication.

The explanation for this discordance is likely to be multi-factorial and to include, to some extent, viral fitness changes that result from the genetic mutations that cause viral resistance to antiretrovirals.

In a study published in AIDS, Investigators from Italy investigated the role of resistance mutations in the HIV reverse transcriptase (RT) and protease (PR) genes as predictive factors in dissociation of immunological and virological responses to HAART. They studied 354 HIV-infected patients with virological failure - defined as a reduction of the HIV-1-RNA level of less than 1 log10 copies/mL after 2 months of treatment or a viral load > 80 copies/mL after 6 months on HAART or any viral rebound after achieving an undetectable viral load - who maintained or failed to maintain a greater than 100 CD4+ T cell increase from baseline.

The patients' median CD4+ T cell count and HIV-1-RNA level at genotyping were 275 cells/mm3 and 4.63 log10 copies/mL, respectively, and they were on HAART for a median of 26 months. A mean increase of 129 CD4+ T cells/mm3 and a mean decrease of 0.09 log10 copies/mL of HIV-1 RNA were observed from the time HAART was started to the time the genotype was obtained. Despite virologic failure, A CD4+ T cell count increase of over 100 cells/mm3 was observed in 159 (45%) patients.

The investigators found that the factors associated with immunological recovery of more than 100 CD4+ T cells/mm3 from baseline despite virological failure were a prolonged time on HAART, a history of an ever-undetectable HIV-1-RNA level, the presence of RT M184V and PR L24I and V82A mutations. In contrast, the probability of immunologic recovery in these patients was significantly decreased by a high HIV-1-RNA level at genotype, a high CD4+ T cell count at baseline, nevirapine exposure and the emergence of the RT Y181C mutation.

The multivariate analysis showed that only the HIV-1-RNA level at genotype, CD4+ T cell count at baseline, and RT Y181C mutation were associated with a reduced probability of sustained immunological recovery, whereas overall time on HAART, an ever-undetectable HIV-1-RNA level and the PR L24I mutation were significant predictors of a persistently elevated CD4+ T cell count. Patients with immunological recovery had lower mean values of HIV-1 RNA at genotype (4.52 versus

4.82 log10 copies/mL; P < 0.01). Patients with RT Y181C mutants had higher mean values of HIV-1 (4.86 versus 4.59 log10

copies/mL; P < 0.01), lower absolute values of CD4+ T cell counts at genotyping (231 versus 313 cells/mm3; P < 0.01) and a lower change of CD4 cell count between baseline and genotyping (+68 versus +142 cells/mm3; P < 0.01).

The authors conclude from these data "Our finding of lower HIV-1-RNA levels in patients with CD4 cell recovery confirmed the role of viral fitness. According to these observations most HIV-1 strains in patients with a discordant viro-immunological response harboured primary and secondary mutations in the protease gene. [The] modest impact on the viral fitness of selected NNRTI mutations, such as K103N and Y181C, is in agreement with the higher HIV-1-RNA level in patients carrying Y181C mutants and with the negative predictive value of Y181C on sustained CD4 cell recovery observed in our study…These observations may have several clinical implications.

It has been observed that among patients with persistent viraemia, despite the presence of reduced drug susceptibility, antiretroviral therapy is associated with sustained immunological benefit, with the maintenance of a viral population with reduced replicative capacity. It is conceivable that these viro-immunological discrepancies could be at least partly mediated by the different effects of mutations on viral fitness.

On one hand, this opens the possibility of considering, in situations of remarkable viro-immunological dissociation and in the absence of valid therapeutic alternatives, the maintenance of drugs selecting for mutations strongly affecting virus fitness. On the other hand, the emergence of a single point mutation able to lead rapidly to broad cross-resistance to the entire NNRTI drug class, in the absence of sustained immunological response (as is the case with Y181C), should suggest a rapid discontinuation of NNRTI after a confirmed virological failure."

Ref: Antinori A; Liuzzi G; Cingolani A et al. Drug-resistant mutants of HIV-1 in patients exhibiting increasing CD4 cell count despite virological failure of highly active antiretroviral therapy. AIDS 2001; 15:2325-2327.

Source:
www.hivandhepatitis.com

DRUG INTERACTIONS

Garlic can impede HIV medication

Researchers have found garlic supplements can cause a potentially harmful side effect when combined with a type of medication used to treat HIV/AIDS. Investigators from the National Institutes of Health (NIH) observed that garlic supplements sharply reduced blood levels of the anti-HIV drug saquinavir. The study results appear this week in an on-line edition of Clinical Infectious Diseases.

"In the presence of garlic supplements, blood concentrations of saquinavir decreased by about 50 percent among our study participants," explains the study's senior co-author Judith Falloon, M.D., an AIDS clinical researcher at the National Institute of Allergy and Infectious Diseases (NIAID). "We saw a definite, prolonged interaction. The clear implication is that doctors and patients should be cautious about using garlic supplements during HIV therapy," she says.

For the first three days of the study, nine healthy, HIV-negative volunteers received doses of saquinavir, one of a class of drugs called protease inhibitors that are effective at slowing the progression of HIV infection. The research team drew samples from the volunteers' blood to measure their baseline levels of saquinavir in the bloodstream.

Next, the volunteers took garlic caplets twice daily for three weeks. When the researchers again analysed blood samples, the average overall levels of saquinavir had decreased 51 percent, and the average maximum concentrations had fallen 54 percent.

Even after a ten-day "wash-out" period with no garlic supplements, when the volunteers again used only the protease inhibitor for three days, their blood levels of saquinavir still averaged about 35 percent lower than the expected baseline amount.

The research paper's lead author is Stephen C. Piscitelli, Pharm D., formerly with the NIH Clinical Center Pharmacy Department and now the Associate Director of Clinical Pharmacology at Tibotec-Virco. Noting that some dietary supplements can cause detrimental interactions with medications, Dr. Piscitelli and his colleagues set out to investigate the effects of a number of herbal therapies. As Dr Falloon explains, "We set out to learn more about these alternative medicine products because there simply are not a lot of clinical data available on them." In their first study, the team found a potentially dangerous interaction between the herbal remedy St. John's wort and the protease inhibitor indinavir.

Garlic became the next focus because of its reputation as a natural cholesterol fighter, which has made it particularly popular for patients whose cholesterol levels have risen due to a side effect from HIV medications. The research team also suspected

a strong possibility of a drug interaction because both garlic and protease inhibitors share the same pathway into the body, a metabolic route known as the CYP450 enzyme system. Exactly how garlic supplements disrupt the uptake of saquinavir is still unclear.

Other questions remain as well, says Dr Falloon. Usually, doctors prescribe saquinavir to be taken together with several anti-HIV drugs, and it is unknown how garlic supplements would affect such a combined drug regimen. “More research is needed in this area, but it’s clear from this study that any patient using saquinavir as the sole protease inhibitor should avoid using garlic supplements,” says Dr. Falloon.

Ref: Piscitelli SC et al. The effect of garlic supplements on the pharmacokinetics of saquinavir. Clinical Infectious Diseases Electronic Edition (December 3, 2001).

C O M M E N T

Caution should also be observed with garlic in food.

PK interaction studies are now needed for other PIs including three way interactions with ritonavir. Additionally studies should be conducted with dietary garlic – food prepared including normal levels of fresh garlic.

Many garlic supplements contain lower levels of the active constituents in garlic than might be expected to be found in prepared foods. It should be assumed, until shown otherwise, that garlic consumed in prepared foods has the same potential for interaction.

Caution needed with nelfinavir and some lipid-lowering drugs

Sean Hosein for Canadian AIDS Treatment Information Exchange

Protease inhibitors can increase levels of lipids, including cholesterol and triglycerides, in the blood, increasing the risk of heart disease. To help reduce the risk of this complication, doctors often encourage their patients to exercise regularly, stop smoking and make changes to their diet. If these changes do not help, doctors then prescribe lipid-lowering drugs, commonly called statins.

Because statins and PIs are often processed by the same enzymes in the gut and liver, these two groups of drugs can interact. Specifically, PIs have the potential to raise or lower levels of statins in the blood, and vice versa. This interaction can increase the risk of new side effects or make pre-existing side effects worse. It is also possible that the effectiveness of PIs can be reduced because of drug interaction(s). To find out about possible drug interactions between PIs and statins, researchers in the US conducted small, short studies on 32 healthy, HIV negative subjects (16 female, 16 male) who were given one of the following statins for one month: atorvastatin (Lipitor) - 10 mg/day; simvastatin (Zocor) - 20 mg/day

After taking one of these drugs for two weeks, subjects also received nelfinavir 1,250 mg twice daily for 14 days. All drugs were taken with food.

Results – statins

The researchers found that there were indeed interactions between nelfinavir and the statins. In the case of atorvastatin, the amount of this drug that was absorbed nearly doubled when it was taken with nelfinavir. When simvastatin was taken with nelfinavir, levels of this statin in the blood were six times greater than when it was not taken with nelfinavir. Levels of these drugs in the blood did not differ between females and males.

Results — nelfinavir

Nelfinavir levels in the blood were not affected by the use of either statin. According to the researchers, the most commonly reported side effect of nelfinavir was diarrhoea — 53% of subjects reported this problem.

What to do

Statins can cause a range of side effects including fatigue and, more seriously, a form of muscle damage called rhabdomyolysis. To reduce the risk of developing this painful complication, the manufacturer of nelfinavir suggests that simvastatin not be used by people who are taking nelfinavir. They also suggest that if atorvastatin is prescribed for nelfinavir-users, it should be used with caution, starting at the lowest dose of 10 mg/day.

Ref: Hsyu P-H, Schultz-Smith MD, Lillibridge JH, et al. Pharmacokinetic interactions between nelfinavir and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors atorvastatin and simvastatin. Antimicrobial Agents and Chemotherapy 2001; 45(12): 3445-3450.

Source:CATIE — Canadian AIDS Treatment Information Exchange. For more information visit CATIE's Information Network at
http://www.catie.ca

comment

These data on nelfinavir and statins was previously presented at the 40th ICAAC, Toronto, September 2000, (presentation 425). It should be remembered that interactions with statins is a feature of the whole class of currently marketed protease inhibitors and caution should be observed with all PI's coadministered with statins.

Further information and data are available from the excellent HIV drug interactions website provided by the Liverpool HIV Pharmacology Group at:

http://www.hiv-druginteractions.org/drug/protease/lipid_lowering.htm

PAEDIATRICS

Syncytium inducing viral phenotype halves thymic T cell production in children

Graham McKerrow, HIV i-Base

HIV-1-infected children with syncytium-inducing (SI) viral strains have CD4+ T cell counts and thymic output levels approximately half as high as those in children with non-SI (NSI) viral strains, according to a new study.

Researchers in Madrid, Spain, compared the thymic production of new T cells in 90 samples from HIV-1-infected children, average age 4.9 years. They also looked at CD4+ T cell levels in the children, and their correlation with thymic output.

Children infected with SI viral strains had CD4+ T cell and thymic output levels approximately half as high as those observed in children with NSI viral strains ($p < 0.001$). Moreover, these differences were independent of viral load (which was similar in the SI and NSI groups), patient age and treatment type, report Drs Rafael Correa and Angeles Munoz-Fernandez, of the Hospital General Universitario "Gregorio Maranon."

In three children followed prospectively, the switch from the NSI to the SI viral phenotype was followed by marked declines in both thymic output and CD4+ T cell levels.

"These results suggest an inhibitory effect of SI viral phenotype on the production of new T cells," the authors say in the October 19th issue of AIDS, "which is independent of viral load and viral replication kinetics." This conclusion is consistent with prior studies indicating that T-tropic (SI) viruses but not M-tropic (NSI) viruses are capable of infecting immature thymocytes.

"It is likely," the investigators believe, "that disease progression in children, which is associated with the appearance of T-tropic viruses, could be due to the inhibition of thymic function produced by these viral strains, which would impede the recovery of lost CD4+ T cells."

"This fact," they conclude, "provides an additional rationale to implement antiretroviral therapies that lead to undetectable viral load levels, even in children with severe CD4+ T cell depletion, with the goal of allowing an adequate thymic function to recover lost T cells."

Ref: Correa R, Munoz-Fernandez MA. Viral phenotype affects the thymic production of new T cells in HIV-1-infected children. AIDS 2001 Oct 19;15(15):1959-63.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11600823&dopt=Abstract

Children with advanced disease who take HAART experience immune reconstitution

Graham McKerrow, HIV i-Base

Children with HIV-1, who have moderate to severe advanced disease and who receive HAART can reconstitute their immune system to the same level seen in children with stable HIV-1 infection, according to a study reported in the October issue of the Pediatric Infectious Disease Journal.

Dr Alicia Johnston and colleagues at Duke University Medical Center, Durham, North Carolina, studied a cohort of 18 HIV-1-infected children, median age 7.4 years. Before these children started HAART, they had moderate to severe suppression of their immune systems as defined by the CDC, with CD4 counts <25% or CDC Category B or C disease. The children received HAART for between four and 33 months.

They were compared with 17 HIV-1-infected children, median age 7.9 years, who had no history of immunosuppression (CD4 > 25%) and no evidence of clinical disease. This second group of children was receiving a non-HAART regimen.

The researchers found that there was no difference in percent CD4+ or percent CD8+ T cells or in maturation markers between the two groups. However, in the group receiving HAART, there was significantly less CD4+ cell ($p = 0.04$) and CD8+ cell ($p = 0.004$) activation when compared with the children not having HAART.

Further, there was no statistical difference between the groups in T cell rearrangement excision circle production, indicative of recent thymic emigrants.

The researchers conclude that if future trials confirm that significant immune reconstruction can truly be achieved in children with clinically stable disease as well as those with advanced disease, then this information could be used either to support the use of HAART in all HIV-infected children or to support the view that delaying therapy results in impressive virologic, immunologic and clinical benefit.

“Continued re-evaluation of the optimal use and timing of antiretroviral therapy in specific populations is needed to address this controversial issue,” they write.

Ref: Johnston AM, Valentine ME, Ottinger J et al. Immune reconstitution in human immunodeficiency virus-infected children receiving highly active antiretroviral therapy: a cohort study. Pediatric Infectious Disease Journal 2001 Oct;20(10):941-6.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11642627&dopt=Abstract

OPPORTUNISTIC EVENTS

New US guidelines for the prevention of opportunistic infections in people infected with HIV

The US Public Health Service and the Infectious Diseases Society of America have drawn up new Guidelines for the Prevention of Opportunistic Infections in Persons Infected with HIV. In the first update since 1999, the guidelines include new advice on drug interactions, screening for other viruses and prophylaxis treatment for OIs.

Major changes to the guidelines include:

- The importance of screening all HIV-infected individuals for hepatitis C virus.
- Additional information about transmission of human herpesvirus 8 infection.
- New information on drug interactions, especially with regard to rifamycins and antiretroviral drugs.
- Revised recommendations for immunization of HIV exposed/infected adults and children.

The new guidelines revise advice on prophylaxis. Higher ratings are 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 three months in response to HAART.

They recommend discontinuing primary toxoplasmosis prophylaxis when the CD4+ T lymphocyte count has increased to >200 cells/μL for three months. Secondary PCP prophylaxis should be discontinued in patients whose CD4+ counts have increased to >200 cells/μL for three months, say the guidelines.

They now say secondary prophylaxis for disseminated MAC may be discontinued in patients with six months increase in CD4+ counts to >100 cells/µL. Secondary prophylaxis for toxoplasmosis and cryptococcosis may be discontinued in patients with sustained (at least six months) increase in CD4+ counts to >200 cells/µL and >100-200 cells/µL respectively.

The full guidelines (PDF format) are available at:

http://www.hivatis.org/guidelines/other/OIs/OIGNov27.pdf

You can request a hardcopy or electronic version of the guidelines by visiting:

http://www.hivatis.org/request.html

Source: HIV/AIDS Treatment Service (HIVATIS)

Incidence and prognosis of AIDS-related lymphoma have improved since the advent of HAART

Graham McKerrow, HIV i-Base

The incidence of systemic and primary brain AIDS-related lymphoma (ARL) has reduced since the introduction of HAART, French investigators report. They also find that prognosis of ARL has improved during this time.

Dr Caroline Besson of Hôpital Necker in Paris and colleagues at sites around France report the findings in the October 15 issue of Blood. They note that while the use of HAART has led to a decrease in the incidence of AIDS-defining illnesses, the consequences of HAART on ARL are “under debate.”

This study compared the incidence and characteristics of ARL before and after the use of HAART in a large population of HIV infected patients recorded in the French Hospital Database on HIV, including 145 patients with proven lymphoma. They compared the periods 1993-4 and 1997-8.

The researchers found that the incidence of systemic ARL decreased during that time from 86.0 per 10,000 person-years to 42.9 per 10,000 person-years. The incidence of primary brain lymphoma has also fallen dramatically between the periods, from 27.8 per 10,000 to 9.7 per 10,000 person-years.

Another analysis shows known HIV history was longer in the second period than in the first among patients with systemic ARL (98 versus 75 months). Patients had higher CD4 counts at diagnosis during the second period (191 versus 63µL). Survival of patients with systemic ARL increased between the periods from 6 to 20 months.

“Therefore,” the researchers conclude, ”the profile of ARL has changed since the era of HAART, with a lower incidence of systemic and brain ARL. The prognosis of systemic ARL has improved.”

Ref: Besson C, Goubar A, Gabarre J, Rozenbaum W et al. Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy. Blood 2001;98:2339-2344.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11588028&dopt=Abstract

Coinfection does not appear to augment TB infectivity

TB from patients coinfected with HIV is not usually more infective than TB from HIV-negative patients, according to researchers in Italy. Mario Cruciani and colleagues at the Center for Preventive Medicine-HIV Screening Center in Verona and the University of Genoa’s Institute of Infectious Diseases conducted a retrospective study to determine “if the relative infectiousness of patients with tuberculosis is enhanced by coinfection with HIV.”

Researchers found no evidence that exposure to HIV patients with drug-sensitive TB was more dangerous than exposure to otherwise healthy TB patients. Cruciani and coworkers reviewed the results of two sets of studies. Data from the first set, comprising six studies of more than 1,200 TB-exposed health care workers, showed that the rate of positive tuberculin skin tests was virtually identical between workers exposed to HIV-positive or HIV-negative patients, according to their report.

Similar conclusions were drawn after examining the second group of 11 studies, which included data from more than 10,000 workers who contacted TB patients at home. In fact, researchers found that skin test positivity was actually less prevalent among health care workers in the cohort who contacted HIV-positive TB patients. “These data suggest that tuberculosis patients with HIV infection are not intrinsically more infectious to their contacts than are HIV negative tuberculosis patients,” Cruciani and coauthors concluded. The full report, “Impact of Human Immunodeficiency Virus Type 1 on Infectiousness of Tuberculosis: A Meta Analysis,” is published in Clinical Infectious Diseases, December 2001;33(11):1922-1930.

Ref: TB & Outbreaks Week (20.11.01)
Source: CDC HIV/AIDS, STD, TB Prevention News Update

PATHOPHYSIOLOGY

Detailed picture emerges of how HIV travels into and out of cells

HIV, must attach itself to cholesterol-rich regions of a cell's membrane before it can do its destructive work, researchers at the National Institute of Allergy and Infectious Diseases (NIAID) have discovered. When the investigators removed cholesterol from the cells, HIV lost much of its ability to produce new virus particles and infect additional cells. These findings provide a more detailed picture of how HIV travels into and out of cells as well as possible ways to block that travel.

"Our research raises the intriguing possibility that widely used cholesterol-lowering drugs might have an effect in humans similar to what we have found in these initial laboratory studies," says Eric Freed, PhD, an investigator in NIAID's Laboratory of Molecular Microbiology, and the senior author of a paper published in the November 20 issue of Proceedings of the National Academy of Sciences.

HIV, like everything else passing into or out of an animal cell, must navigate the cell's complex double-walled outer membrane. Much like a bog, a cell membrane contains some areas of relatively solid material while other regions are more fluid. Among the features of this constantly shifting landscape are small, cholesterol-rich patches called rafts, which are more solid than the surrounding membrane and are able to move about like a raft on water.

Rafts are believed to be most concentrated at points of cell-to-cell contact in the immune cells that HIV targets for infection. Any mechanism that helps HIV find and attach to rafts would help the virus spread. Conversely, even a modest degree of disruption could slow the virus' spread because it would hinder the virus' ability to enter and leave its host cells.

Scientists have known for some time that an HIV protein called Gag must attach to the inner surface of the cell membrane before new viruses can be produced. Scientists also suspected that Gag's attachment to the membrane is not random, but rather targets specific regions of the cell surface. The new research shows their suspicions were correct.

Dr Freed and his co-author Akira Ono, PhD, first established that Gag does indeed attach to rafts. They then created several mutant forms of Gag and learned that two pieces of the protein are required for successful attachment. Finally, the investigators turned to the key question of what happens when HIV is kept off the rafts.

To determine this, they depleted cholesterol from rafts using two compounds, one of which removes cholesterol rapidly from the cell surface and one that inhibits cholesterol synthesis. When used alone, each compound significantly reduced HIV's ability to form particles that could infect new cells. Applied simultaneously to virus-producing cells, the compounds almost completely abolished HIV's power to replicate.

"Our findings are clear evidence that Gag-raft association is a critical step in HIV replication," says Dr. Freed. "Additional experiments are needed to determine whether this interaction can be interrupted therapeutically to treat HIV-infected people."

Ref: Ono A, Freed EO. Plasma membrane rafts play a critical role in HIV-1 assembly and release. Proceedings of the National Academy of Sciences 2001 Nov 20;98(24):13925-30.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11717449&dopt=Abstract

Source: National Institute of Allergy and Infectious Diseases press release.

High levels of HIV replication shut down anti-HIV immune responses

New research suggests that HIV-specific T cells persist in infected individuals, but high virus levels can diminish the ability of those cells to respond to infection. The report sheds new light on how HIV evades the immune system and establishes long-term infections. The research appears in the November 20, 2001 issue of the Proceedings of the National Academy of Sciences.

"HIV infection not only destroys the body's resistance to other pathogens, but it can manipulate the immune system for its own survival," says Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID). "This research provides some important clues to how the virus accomplishes that goal."

In chronic viral infections, CD4+ T cells are required for the immune system to keep virus levels in check. In HIV-infected people, however, few anti-HIV CD4+ T cells proliferate when exposed to viral proteins. Researchers have not known if the absence of a proliferative T-cell response occurs because the virus destroys or merely inactivates HIV-specific CD4+ T cells.

NIAID's Andrew McNeil, MD, and Mark Connors, MD, led a study to answer that question. The investigators studied the T cells of three groups of patients: those with progressive HIV infection; a rare subset of individuals with long-term, untreated infection but with viral RNA levels consistently below the level of detection (long-term nonprogressors); and patients on antiretroviral

therapy who stopped taking their drugs long enough for virus levels to rebound.

All three groups had equal numbers of HIV-specific CD4+ T cells, indicating the cells were not destroyed by the virus. The HIV-specific CD4+ T cells of people with progressive disease, however, did not respond to the virus by proliferating, suggesting they had somehow been turned off.

To examine the cause and effect relationship between proliferative T-cell responses and immune control over the virus, Drs McNeil, Connors, and their colleagues turned to the patients who showed anti-HIV T-cell proliferation while taking antiretroviral drugs. The investigators reasoned that if those T cells were keeping HIV levels low, they should continue to do so even if therapy were interrupted. When the researchers stopped the drugs, however, virus levels rebounded in each of the patients. In those individuals, anti-HIV CD4+ T cells were present but lost their ability to proliferate as virus levels increased. Furthermore, the cells maintained their inactive state until antiretroviral drugs brought virus levels back under control.

The results suggest that the loss of HIV-specific T-cell proliferation may not be a cause, but rather is an effect, of high virus levels. Such proliferation, which is present in long-term nonprogressors, therefore does not necessarily predict immune control over the virus.

“This presents a good news/bad news scenario,” says Dr Connors. “The good news is that HIV-specific CD4+ T cells are not completely deleted; the bad news is that measuring the activity or even the frequency of those cells is not necessarily a good predictor of long-term virus control.”

The results suggest that long-term interruptions in antiretroviral therapy may not be the best way to stimulate anti-HIV immune responses. The results also provide some clues to how HIV disrupts the immune response to itself and responses to other pathogens.

Ref: McNeil AC, Shupert WL, Iyasere CA et al. High-level HIV-1 viremia suppresses viral antigen-specific CD4+ T cell proliferation. Proceedings of the National Academy of Sciences 2001 Nov 20;98(24):13878-83.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11717444&dopt=Abstract

Source: National Institute of Allergy and Infectious Diseases press release.

Natural killer cell activity varies with viral burden in HIV-1 infection

Receptor expression and activity of natural killer (NK) cells vary with viral burden in patients infected with HIV-1, according to a report in the November Journal of Medical Virology.

Natural killer (NK) cells play an important role in controlling viral infections, particularly herpes virus infections in humans, the authors explain. Aberrant expression of NK cell receptors may result in ineffective immune responses against such viruses and against tumours.

Dr Ali Ahmad from the University of Montréal in Québec, Canada and colleagues studied the modulation of NK activity and the expression of NK receptors in 36 adults infected with HIV-1 who had AIDS. Thirty patients were receiving highly active antiretroviral therapy.

The average NK activities of the patients were significantly less than those of healthy controls, the authors report. Surprisingly, the researchers note, the NK activities showed a clear tendency to increase with increasing HIV-1 viral burden. NK activity showed a negative trend with increasing CD4+ T-cell counts, the report indicates.

HIV-1 infected patients had decreased percentages of cells expressing CD56 and CD16 but increased percentages expressing CD8, GL183, CD94, and CD57, the investigators say. There were also significant perturbances in NK receptor expression in CD8+ cytotoxic lymphocytes.

“To our knowledge,” the researchers write, “this is the first report that suggests a decrease in NK cell activity after suppression of viral replication in HIV-infected/AIDS patients. Equally surprising was the negative correlation of NK activity with CD4+ T-cell counts of the patients.”

“Taken together,” the authors conclude, “these data suggest a complex, multifaceted interaction with viral replication, its gene products, and different immune parameters.”

The investigators add, “the decrease in NK activity accompanying a decrease in plasma HIV burden of HIV-infected/AIDS patients, shown here, may necessitate measures to enhance innate immunity of these patients.”

Ref: Ahmad R, Sindhu ST. Modulation of expression of the MHC class I-binding natural killer cell receptors, and NK activity in relation to viral load in HIV-infected/AIDS patients. Journal of Medical Virology 2001 Nov;65(3):431-40.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11596074&dopt=Abstract

IMMUNOLOGY

MDMA: Acute effects of ecstasy on T-cell numbers and function

Sean Hosein, for Canadian AIDS Treatment Information Exchange

The popular recreational drug ecstasy — or more simply "E" — causes users to experience feelings of bliss. Although users perceive ecstasy as safe, this drug does have a dark side. There have been worrying reports of long-term memory problems among some former ecstasy users. More recently, researchers in the European Union have been studying the impact of ecstasy on the immune systems of mice and people and have found some troubling data.

Study details

Researchers enrolled 17 healthy (HIV-uninfected) male subjects for a series of short, placebo-controlled studies of ecstasy. Subjects received 100mg ecstasy once or twice over a period of 24 hours. Blood samples were collected before, during and after the study.

Results: a single dose

The researchers found that a single dose of ecstasy (100mg) taken by mouth caused a dramatic fall in the level of immune system cells called T cells, which are needed to help fight infections. The number of a specific group of T cells, called CD4+ cells, decreased by about 30% within hours after a single dose of ecstasy. Fortunately, within a day after taking this dose, CD4+ cell levels returned to normal.

Results: two doses

Among subjects who received two doses of the drug, four hours apart, the decline in CD4+ cells was even more serious, reaching a level 40% below normal. Although a day later T-cell levels rose, they did not return to normal.

Another important finding is that ecstasy clearly reduced the ability of T cells as well as other immune system cells to fight infections.

Why is ecstasy not immune friendly?

Perhaps these results should not be surprising as ecstasy is chemically related to another group of chemicals called amphetamines. This group of drugs does not enhance the health of the immune system. The research team also found that exposure to ecstasy causes the body to produce increased amounts of the hormone cortisol. This hormone probably caused the CD4+ cell count to temporarily fall because these cells moved from the blood to the lymph nodes and tissues. They returned to the blood once cortisol levels returned to normal. Higher than normal cortisol levels may also have been the reason that the immune cells' ability to fight infections was reduced. In people with HIV/AIDS who use ecstasy, the drug therefore has the potential to increase levels of HIV.

Furthermore, ecstasy can rise to dangerous levels among patients who also use anti-HIV drugs known as protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

Another point to consider is that the researchers used relatively pure ecstasy. In the real world, it is not uncommon to find ecstasy blended with a small amount of amphetamine or LSD. Unlike the situation with licensed drugs, no independent agencies have the authority to conduct quality control tests to ensure that chemical contaminants are removed from the final product. Nor are there any agencies that have the power to force ecstasy manufacturers to conduct studies on the impact of this drug on the health of users. Given the increasing popularity of ecstasy, harm reduction experts have their work cut out for them.

References:

1. Pacifici R., Zuccaro P., Farré M., et al. Effects of repeated doses of MDMA ("Ecstasy") on cell-mediated immune response in humans. Life Sciences 2001; 69:2931-2941.
2. Connor T.J., Connelly D.B. and Kelly J.P. Methylenedioxy-methamphetamine (MDMA; "Ecstasy") suppresses antigen specific IgG2a and IFN-gamma production. Immunology Letters 2001; 78(2): 67-73.

Source: CATIE — Canadian AIDS Treatment Information Exchange.

For more information visit CATIE's Information Network at
http://www.catie.ca

METABOLIC ADVERSE EVENTS

Elevated blood pressure in subjects with lipodystrophy

Simon Collins, HIV i-Base

The importance of elevated blood pressure (hypertension) and the relationship with lipodystrophy, which has not previously been researched, was addressed by Sattler and colleagues from University of Southern California. This was a retrospective analysis from records of 42 consecutive people with diagnosed lipodystrophy who had been referred to a metabolic disorders clinic from March 1998 to August 1999.

For each symptomatic patient, blood pressure was assessed from six months prior to the time of initiation of a PI or NNRTI containing regimen (23±16 measurements over 21±11 months). 42 age- and sex-matched HIV-positive people using similar HAART but without diagnosed lipodystrophy and 13 HIV-negative people were used as control groups. Family history of hypertension was taken into account in the final analysis (higher in the cohort at 62% versus 36% for HIV-positive control).

Elevated blood pressure was defined as three or more readings in medical records showing diastolic blood pressure (DBP) >90mmHg or systolic values >140 mgHg. Mean values of the three highest readings over the study period were used to compare to the HIV-positive control group.

Lipodystrophy symptoms were present in the following percentage of the group: lipoatrophy 88% (peripheral limb 69%, facial 57%, buttocks 55%), accumulation 69% (abdominal 57%, buffalo hump 24%, multiple lipoma 7%, breast 7%) and metabolic 86% (fasting TG≥200mg/dl 33%, HDL≤35mg/dl 48%, total cholesterol≥200mg/dl 63%).

Although the HIV-positive control group were selected on the basis that they had no apparent lipodystrophy symptoms, baseline body measurements and blood lipid levels were similar to the study cohort.

However, the proportion of people with elevated BP was higher in the cohort (74%) than in the HIV-positive controls (48%). Diastolic PB increased in 71% versus 43% and systolic BP in 43% versus 21% respectively (p=0.02 for each).

There was a higher incidence of family history of hypertension in a first degree relative in the cohort compared to the HIV-positive control group (62% versus 36%) and when the data were controlled for this the difference in blood pressure between the two groups diminished, although the number of subjects with three elevated SBP or DBP results, the proportion of readings elevated, and mean of three highest DBP were all higher in the lipodystrophy group and this was statistically significant ($P<0.05$).

Waist-to-hip ratio (WHR) significantly correlated with SBP (p=0.01) and increased WHR occurred more frequently in patients with elevated blood pressure than those with normal blood pressure (34% versus 16%) although the actual number of patients involved was small. WHR correlated with SBP in the lipodystrophy cohort compared to HIV-negative controls. There was also a high tendency for correlation between fasting triglycerides and SBP in HIV-positive patients in either group.

Because the HIV-positive control group actually had a similar rate of clinical (but undiagnosed) lipodystrophy to the lipodystrophy cohort there was not really a non-lipodystrophy HIV-positive control. However in both HIV-positive groups the proportion of people with elevated SBP was greater than the proportion with elevated DBP and isolated elevation of SBP is an independent risk factor for cardiovascular complications.

Only one woman was included in the study so further studies are required in more representative cohorts in order to understand the relationship between blood pressure, HIV and lipodystrophy.

Non-pharmacologic interventions such as diet, exercise and reduced salt and alcohol intake were advocated for patients with more than three SBP readings 140-159 mmHg and drug therapy was used for higher levels or non-responsive cases.

Ref: Sattler FR, Qian D, Louie S et al – Elevated blood pressure in subjects with lipodystrophy. Journal of AIDS 2001 Oct 19;15(15):2001-10.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11600829&dopt=Abstract

C O M M E N T

The study provided supportive evidence that lipodystrophy can contribute to risk factors for hypertension and that as hypertension in itself is a risk factor for myocardial infarction, stroke, renal failure and peripheral arterial disease. The study also showed that is may be common for elevated levels to continue for extended periods (over two years).

Fat distribution is strongly tied to metabolic disturbances in HIV lipodystrophy

In HIV-infected patients with lipodystrophy, body fat distribution is strongly associated with the metabolic disturbances that accompany this disorder, according to a recent report. In addition, resting energy expenditure (REE) is increased in these patients.

Dr Lisa A. Kosmiski, from the University of Colorado Health Sciences Center in Denver, and colleagues assessed the body fat composition, metabolic profile, and REE of 32 HIV-infected patients. The study group included 14 protease inhibitor (PI)-treated patients with lipodystrophy, 13 PI-treated patients without lipodystrophy, and 5 PI-naïve patients without lipodystrophy.

Lipodystrophy patients were significantly less sensitive to insulin than other patients, the authors note. Among patients without lipodystrophy, PI-treated patients tended to be less insulin sensitive than PI-naïve subjects.

In lipodystrophy patients, measures of central obesity correlated strongly with metabolic disturbances. The percent of total body fat present in extremities also correlated strongly with metabolic changes, but it appeared to be protective against metabolic abnormalities.

Multivariate analysis revealed that the amount of visceral adipose tissue independently predicted insulin sensitivity and HDL-cholesterol levels, the investigators state in the October 19th issue of AIDS.

REE was significantly higher in the lipodystrophy group than in the other groups, the researchers state. In addition, insulin sensitivity was a strong independent predictor of REE in the lipodystrophy patients.

In a related editorial, Dr David Nolan and Dr Simon Mallal from the Royal Perth Hospital in Western Australia comment that "there is now abundant evidence that HIV PIs as a class make a powerful independent contribution to the 'metabolic syndrome' that accompanies the long-term use of highly active antiretroviral therapy regimens."

Drs Nolan and Mallal note that the current findings "move us one step closer to elucidating the proximal pathogenic mechanisms of the metabolic syndrome induced by the PI class, which in turn will clarify the relationship between nucleoside analogue reverse transcriptase inhibitors and PIs in the pathogenesis of the lipodystrophy syndrome as a whole."

Ref: Kosmiski LA, Kuritzkes DR, Lichtenstein KA et al. Fat distribution and metabolic changes are strongly correlated and energy expenditure is increased in the HIV lipodystrophy syndrome. AIDS 2001 Oct 19;15(15):1993-2000.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11600828&dopt=Abstract

Source: Reuters Health

Eating more often can reduce cholesterol levels

Eating frequently is associated with lower blood cholesterol concentrations, finds a study in this week's BMJ, suggesting that we need to consider not just what we eat but how often we eat.

Over 14,000 men and women aged 45-75 years were asked "How many times a day do you eat including meals, snacks, biscuits with coffee breaks etc?" Participants were then classified into five categories of eating frequency and concentrations of blood fats (lipids) were measured.

Cholesterol concentrations were approximately 5% lower in men and women who ate six or more times a day compared with those who ate once or twice a day, despite higher intakes of energy, including fat, in people who reported eating more frequently. This association was still present after accounting for body mass index, physical activity, cigarette smoking, and dietary intake.

Although not large, this difference in cholesterol concentration is comparable to that achieved in studies involving alteration of intake of dietary fat or cholesterol. It is also associated with reductions in coronary heart disease ranging from 10% to 21%, say the authors.

If applied population-wide, such reductions might have a substantial impact, particularly in older people, who have higher rates of heart disease, they conclude.

Ref: Titan SM, Bingham S, Welch A et al. Frequency of eating and concentrations of serum cholesterol in the Norfolk population of the European prospective investigation into cancer (EPIC-Norfolk): cross sectional study. BMJ 2001 Dec 1;323(7324):1286.

Full text at:
http://bmj.com/cgi/content/full/323/7324/1286

OTHER NEWS

TRAIL ligand induces apoptosis of HIV-infected cells in-vitro

Sean Hosein for Canadian AIDS Treatment Information Exchange

The use of highly active antiretroviral therapy (HAART) has helped to put AIDS into remission for many people who have symptoms of HIV/AIDS. Unfortunately, taking HAART often means swallowing a handful of pills at regular intervals several times daily, sometimes with food and water restrictions. HAART can also cause side effects, some of which are unpleasant while others are more serious.

Attempts at a cure

Perhaps the most disappointing aspect of HAART is that it does not rid the body of HIV. Proof of this lies in studies where people with HIV/AIDS stop taking their medication (these "drug holidays" are commonly called Structured Treatment Interruptions, or STIs). In such cases virus levels have often surged into the detectable range. HAART is unable to cure HIV infection because the virus can lie low, hiding in some cells of the immune system that are at rest. Because the virus can keep a low profile in resting cells, the immune system does not know that these cells are infected and does not destroy them, allowing HIV to persist. As well, anti-HIV drugs do not work well in resting cells or another group of immune cells called macrophages, which are also infected by HIV.

Although there have been attempts to purge the body of HIV using a combination of HAART and IL-2 (interleukin-2), these have not been successful. Now a team of Canadian scientists has taken a different approach to destroying HIV-infected cells that may be worth testing in HIV positive people.

On the TRAIL, in the lab

Researchers at the University of Ottawa, working in the laboratory of Dr. Andrew Badley, have been studying ways of killing HIV-infected cells using a compound called TRAIL (TNF-related apoptosis-inducing ligand). Technicans collected blood samples from patients who had been taking HAART and who had low levels of HIV in their blood (fewer than 50 copies) for at least a year. Immune cells were removed from the blood samples and exposed to TRAIL in the test-tube for about 12 hours. In analysing their results, the researchers found that HIV-infected T cells (CD4+ and CD8+ cells) had died, while most of the HIV-negative cells lived. Researchers also found that TRAIL was able to kill other groups of HIV-positive cells such as macrophages and memory cells.

How TRAIL works

TRAIL works by causing HIV-infected cells to commit suicide — a process known as apoptosis. What is novel about the Canadian research is that it takes advantage of a natural process and it also works in macrophages. This latter point is important because currently available therapies, and a few in the pipeline, don't work well in these cells, allowing HIV infection to persist. In theory, TRAIL should be low in toxicity. Studies in healthy mice and monkeys suggest that most versions of TRAIL are not harmful to major organs (liver, kidneys, heart, bone marrow).

What's next

According to the Ottawa researchers, the next step is to test TRAIL in monkeys infected with a an artificial but lethal virus called SHIV (simian HIV). Infection with SHIV causes AIDS to develop quickly in monkeys. These experiments are underway in the U.S. If they are successful, then studies with TRAIL given intravenously to HIV patients will be next. Because TRAIL also has anti-tumour activity, it is being tested in animals with cancer.

Ref: Lum JJ, Pilon AA, Sanchez-Dardon J et al. Induction of cell death in human immunodeficiency virus-infected macrophages and resting memory cd4 t cells by trail/apo2l. Journal of Virology. 2001 Nov;75(22):11128-36.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11602752&dopt=Abstract

Source: From Canadian AIDS Treatment Information Exchange (CATIE). For more information visit CATIE's Information Network at http://
http://www.catie.ca

DHEA replacement therapy improves quality of life

Michael Greer, for AIDSWEEKLY Plus

Treatment with the adrenal hormone DHEA can be beneficial for patients in advanced stages of HIV infection, researchers in France report.

“Plasma levels of dehydroepiandrosterone sulphate (DHEA-S) decrease with the progression of HIV disease,” according to Christophe Piketty and colleagues at Hopital Europeen Georges Pompidou, Hopital Trousseau, and Hopital Paul Brousse in Paris, and Hopital Bicetre in Le Kremlin Bicetre. Low levels of DHEA have been linked to poor immune function and depression.

Piketty and coworkers found that DHEA replenishment therapy could significantly improve HIV patients’ quality of life.

The researchers evaluated the effects of 50 milligrams of DHEA a day in 32 volunteers with advanced HIV disease. Plasma levels of DHEA-S, the circulating form of DHEA, rose significantly in treated patients but fell slightly in control patients, they said.

Patients treated with DHEA also displayed significant improvements in the mental health and health-related distress components of the Medical Outcomes Study HIV Health (MOS-HIV) Survey, improvements not seen in placebo-treated participants, study data showed. No adverse effects linked to DHEA therapy were observed.

The number of CD4 cells was not affected by DHEA administration.

“The administration of DHEA in patients with advanced HIV infection results in improved mental function scores as assessed by the MOS-HIV quality of life scale,” Piketty and coauthors concluded.

Ref: Piketty C, Jayle D, Leplege A et al. Double-blind placebo-controlled trial of oral dehydroepiandrosterone in patients with advanced HIV disease, Clin Endocrinol (Oxf) 2001 Sep;55(3):325-30.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11589675&dopt=Abstract

Source: AEGIS.
http://ww2.aegis.org/pubs/aidswkly/2001/AW011104.html

C O M M E N T

Further information on DHEA and HIV (all from TreatmentUpdate 114 - 2001 January; Volume 12 Issue 10)

DHEA — Background

http://www.aegis.com/pubs/catie/2001/cate11405.html

DHEA — Cautions and concerns

http://www.aegis.com/pubs/catie/2001/cate11402.html

DHEA for depression?

http://www.aegis.com/pubs/catie/2001/cate11403.html

Changes in DHEA levels in people taking anti-HIV therapy

http://www.aegis.com/pubs/catie/2001/cate11404.htm

Updated: Public Health Service task force recommendations for use of antiretroviral drugs in pregnant HIV-1-Infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States.

Updated: Safety and toxicity of individual antiretroviral agents in pregnancy

The Update Perinatal HIV Guidelines along with the Updated Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy document were updated on December 5, 2001.

The updated documents include information on the use of Tenofovir DF relevant to pregnancy. Specifically, the updates include Table 2 of the Perinatal Guidelines and pages 87, and 89-90 of the Safety and Toxicity document.

Both documents can be viewed or downloaded at:

http://www.hivatis.org/trtgdlns.html#Perinatal.

Or, if you prefer, you can request a hardcopy or electronic version of the guidelines by visiting

http://www.hivatis.org/request.html.l

Medicinal plant 'fights' AIDS

Carolyn Dempster, for BBC News

A South African indigenous medicinal plant may hold the key to the treatment of millions of poor people living with HIV and Aids, helping them relieve the symptoms of Aids.

For the first time in South Africa's medical history, the plant, Sutherlandia Frutescens, sub-species Microphylla, is to undergo clinical trials to assess its immune-boosting properties.

The Medical Research Council will conduct the trials early next year and results are expected within three to six months.

Anecdotal evidence is already mounting, suggesting that this plant can improve the quality of life of thousands of people both with HIV and full-blown Aids.

Sutherlandia Frutescens grows wild in the Western Cape and in the hills of Zululand.

Cancer bush

A particular variety of the plant has been used for centuries as a potent medicine by South Africa's indigenous San people who call it "Insisa" - the one that dispels darkness. They used it as an energy booster and a powerful anti-depressant.

Zulu sangomas or traditional healers know it as "Unwele", the great medicine that was used to ward off the effects of the devastating 1918 influenza pandemic which claimed 20 million lives worldwide.

The Tswana people know it as "Mukakana" for its power in treating gonorrhoea and syphilis, while the Afrikaners call it the "Kankerbossie" or cancer bush, because of its properties in treating people suffering with internal cancers and wasting.

Molecular combination

A local company specialising in the development of indigenous plant medicines, Phyto Nova, first started researching the bio-chemical properties of Sutherlandia about three years ago.

A multi-disciplinary team headed by Dr Nigel Gericke, a botanist, medical doctor and indigenous plant specialist, found that Sutherlandia contained a powerful combination of molecules which have been identified and used in the treatment of patients with cancer tuberculosis, diabetes, schizophrenia and clinical depression and as an antiretroviral agent.

Phyto Nova were so convinced that Sutherlandia could be used as a tonic for people infected with HIV and Aids, that they contracted farmers to plant acres of the bush, to prevent wild supplies being over-harvested. They have been manufacturing high quality Sutherlandia tablets, gel and powder.

Having determined that the product was safe when administered with a balanced food diet, the company distributed Sutherlandia to Aids patients.

Quality of life

"Anecdotally we are accumulating evidence that wasted patients with Aids, TB and cancer pick up weight, regain energy and appetite," says Dr Gericke."The claim we are making on the basis of this, is that we can significantly and dramatically improve

the quality of life of many ill Aids patients... We are certainly not making the absurd claim that Sutherlandia is a cure-all or a cure for Aids."

Whatever comes of the clinical trial, word of the plant's properties is already spreading among South Africa's traditional healers. At the same time as Phyto Nova was conducting its research, one of the country's most venerated traditional healers, Dr Credo Mutwa, 80, was using Sutherlandia to treat Aids patients.

"My aunt Minah, who is 103 years old, told me that we should use the great medicine against Aids," said Dr Mutwa. "I said to her: 'But aunt, the white people tell us there is no cure for this disease'. "And my aunt said: 'For every disease there is a treatment. Try this medicine'. And I tried it."

'Near-miraculous'

"I have treated people who were told by the doctors at the hospital to 'go home and die' and they are still alive today, three years after they should have died. This plant is near-miraculous, I can say that with certainty," he says.

Testimony to the efficacy of the plant continues to mount.

Anne Hutchings, an ethno-botanist and lecturer at the University of Zululand has been using Sutherlandia, together with a range of other indigenous plant medicines, to treat Aids patients who attend the weekly Aids clinic at Ngwelezane Hospital. She has 176 patients who all testify that Sutherlandia has helped them to live a fuller, healthier and more productive life.

No response

In the Northern Cape town of Kuruman, nurse and sangoma, Virginia Rathele is using Sutherlandia at her clinic to treat more than 300 Aids patients. She says an integral part of the treatment is to tell patients to eat healthily. "Sutherlandia does not work properly just on a diet of porridge. You have to have vegetables," she said.

One client, who weighed 26kg and was close to death in April this year, now weighs 45kg and is helping Ms Rathele run the clinic. Patents cannot be taken out on plants which have well-documented folk use, which means that Sutherlandia should remain accessible to anyone.

At present, one month's supply of Phyto Nova tablets costs a little under $2.50 and two months' supply of the powder form of the medication can be bought for less than 50 cents.

Phyto Nova has approached the South African Government in a bid to persuade them to grow the plant on a massive scale for use in public health treatment.

So far they have had no response.

Source: BBC News Online.
http://news.bbc.co.uk/hi/english/world/africa/newsid_1683000/1683259.stm

C O M M E N T

Sutherlandia contains high levels of canavanine, pinitol and gaba – already individually patented by drug firms as treatments for cancer, fungal infections, diabetes and anxiety.

ON THE WEB

Reports of progress towards understanding how some people appear to fight off HIV

TAGLine Volume 8 Issue 9, November 2001

In the United States, long-term studies of HIV-infected and high-risk people have mainly involved gay men–the group most heavily affected in the epidemic's early years. But a continent away, in the Pumwani district of Nairobi, a group of just over 100 women have become well-known to HIV researchers around the world by offering tantalizing evidence that the immune system can, in rare cases, fight off HIV. Richard Jeffreys prepared this report. Two related articles, "Holding HIV At Bay: What Keeps Exposed Babies Uninfected?" and ""HLA Genes and Immunity" appeared in the September issue of IAVI Report and

can also be found at:
http://www.iavi.org

Full text at:

http://www.aidsinfonyc.org/tag/taglines/0111.html#3

Conference report from the 39th IDSA

Antiretroviral agents and response to therapy

Data presented at IDSA should heighten physicians' caution about initiating antiretroviral therapy in patients with higher CD4+ cell counts, writes Joseph J. Eron Jr, MD.

Medscape, 2001. (C) 2001 Medscape, Inc.
http://hiv.medscape.com/44987.rhtml

Optimising long-term HIV treatment strategies through a greater understanding of disease pathogenesis

Optimising antiretroviral therapy for individual patients requires an understanding of the multiple factors that determine treatment outcomes, such as viral coinfections, host genetics, and viral diversity, writes Steven G. Deeks, MD.

Medscape, 2001. (C) 2001 Medscape, Inc.
http://hiv.medscape.com/44988.rhtml

Metabolic complications and adverse drug reactions in HIV

It seems increasingly apparent that the choice of antiretroviral therapy must be influenced by factors other than HIV, and in particular by cardiovascular risk factors, writes William G. Powderly, MD.
Medscape, 2001. (C) 2001 Medscape, Inc.
http://hiv.medscape.com/44989.rhtml

Update: incidence, diagnosis, and clinical manifestations of HIV-related OIs

Opportunistic infections continue to receive attention in terms of their incidence, diagnosis, and clinical manifestations, writes Henry Masur, MD.
Medscape, 2001. (C) 2001 Medscape, Inc.
http://hiv.medscape.com/44990.rhtml

Immune reconstitution diseases associated with antiretroviral therapy

What's new concerning the inflammatory immune reconstitution diseases observed in some patients soon after initiating potent antiretroviral therapy? Find out in this easy-to-navigate compilation of MEDLINE and conference abstracts compiled by Martyn French, MD, FRCP, Royal Perth Hospital, Australia.
Medscape, 2001. (C) 2001 Medscape, Inc.
http://hiv.medscape.com/45160.rhtml

Developing an HIV/AIDS therapeutic agenda for resource-limited countries

Report from the conference convened by the IDSA concluded that therapeutic research in resource-limited countries requires a unique paradigm, with emphasis placed on sustainable interventions and ethical conduct of the research.
Medscape, 2001. (C) 2001 Medscape, Inc.
http://hiv.medscape.com/45576.rhtml?srcmp=aids-113001

Review: Treatment of chronic hepatitis

Paul J Gow and David Mutimer, BMJ 2001;323 1164-1167

Viral hepatitis is the major cause of chronic liver disease worldwide. An estimated 300 million people are carriers of the hepatitis B virus, and 120 million are infected with hepatitis C. Untreated, these infections may progress to cirrhosis, liver failure, and hepatoma. Public health measures to limit new infection, including immunisation against hepatitis B and screening of blood

products for HBV and HCV viruses, have now been implemented in most developed countries and are being implemented in many developing counties.

This review focuses on the treatment of chronic hepatitis B and C, which has undergone dramatic improvement in the past few years.

http://bmj.com/cgi/content/full/323/7322/1164

HIV i-Base and Royal Free Centre for HIV Medicine

MEETING ANNOUNCEMENT

Facial Lipoatrophy, Polylactic Acid (*New Fill*) and access to treatment in the UK

Thursday 24th January 2.00pm - 5.30pm

Royal Society of Medicine, 1 Wimpole St, London

How prevalent is facial lipoatrophy?
What is the impact on quality of life snd
current responses from UK clinics?
Is NewFill an effective treatment?
When can patients expect this as a treatment option?

Progressive facial fat loss (lipoatrophy) is an increasing problem for people with HIV and can have a dramatic and negative impact on the quality of life. Although the mechanism for this change is not understood there is a general recognition that the multifactorial causes include both HIV treatments and HIV itself.

Recent reports of a new corrective treatment (Polylactic Acid injections, marketed under the trade name *NewFil*l) have provided evidence that reversal of facial fat loss may be possible at relatively low cost. *New Fill* is a compound approved by the European Agency for the Evaluation of Medicinal Products, and has none of the complications of alternative repair procedures such as silicone or collagen.

This open meeting for clinicians, healthcare workers, advocates and HIV-positive people will include discussions and presentations on:

- An overview of current approaches to facial atrophy in UK clinics: which procedures, if any, are available; demand for treatment, protocols for referral to private medicine
- 24-week results from Dr Aubron-Olivier, Hôpital Pitie Salpetriere. Paris
- UK Study run at the Chelsea and Westminster Hospital
- Report on positive and negative affects on quality of life
- from HIV-positive people who have used this treatment
- Current structure for funding/reimbursement

For further information please contact:

Simon Collins at i-Base: 020 7407 8488 or
Mike Youle at RFH: 020 7830 2589

Registration is free for clinicians, healthcare professionals, HIV-positive people and community.

Please reserve your place early using the fax-back form below as places are limited - or contact the i-Base office on 020 7407 8488.

HIV i-Base & Royal Free Centre for HIV Medicine

Fax-Back Registration Form

Facial Lipoatrophy, Polylactic Acid (*New Fill*) and access to treatment in the UK

Thursday 24th January 2002

2.00pm - 5.30pm

Royal Society of Medicine, 1 Wimpole Street, London W1

Please reserve a place for me for the above HIV i-Base meeting.

Name: _____

Position/Organisation: (if applicable) _____

Address: _____

_____

_____

Telephone: _____ Fax: _____

e-mail: _____

Registration for HIV i-Base meetings is free for doctors, nurses, pharmacist s and healthcare workers and to HIV-positive people, community and community press. Please contact the HIV i-Base office for details of industry attendance rates.

This meeting is likely to be very popular and we recommend early registration.

Please fax to HIV i-Base on:

020 7407 8489

HIV i-Base, Third Floor East, Thrale House, 44-46 Southwark Street, London SE1 1UN
T: +44 (0) 20 7407 8488 F: +44 (0) 20 7407 8489 email: admin@i-Base.org.uk website: http://www.i-Base.org.uk

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Third Floor East, Thrale House, 44-46 Southwark Street, London SE1 1UN
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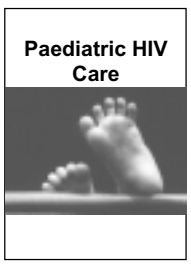
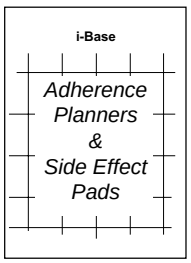
These other publications are also available. All publictions are provided free of charge.





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

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

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

Positive Treatment News (PTN) *from Winter2001*
1 ☐ 5 ☐ 10 ☐ 25 ☐ 50 ☐ 100 ☐ Other_____

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

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_____

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