

# The amfAR Treatment Insider

*Report from the  
7th Conference on  
Retroviruses and  
Opportunistic Infections  
Jan. 31 - Feb. 2, 2000*

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## *And Now for the Long View*

The first protease inhibitors were approved four years ago. Just months before, approval of 3TC bolstered dual nucleoside analog therapy. Separated from each other, PIs and dual NAs each had an obvious weakness. The rapidly mutating HIV quickly developed drug resistance in response to their use. But together they worked like magic. When a protease inhibitor was combined with two nukes, HIV replication plunged below the level of detection then feasible. It seemed virtually impossible for the virus to evolve drug resistance to three drugs at once. All we would need do is “hit hard, hit early” with the new highly active antiretroviral therapy, dubbed HAART, to achieve viral eradication.

This winter’s edition of the Conference on Retroviruses and Opportunistic Infections, a kind of annual national AIDS conference that focuses on medical research, was a chance to review what we have learned since the advent of HAART. Four years of HAART have caused us to back away from the previous optimism. True, disease and deaths remain drastically reduced, but “viral eradication” has proved a mirage. Low levels of HIV replication persist despite HAART. Life-long treatment seems mandated.

As time drags on, HIV increasingly evolves to escape therapy, just as it used to. Patients’ growing inability to rigorously adhere to HAART’s arduous pill-taking schedules

often accelerates the evolution of drug resistance. There is growing awareness, too, of the poorly understood long-term toxicities of treatment. These pose still uncharted dangers on their own and further impede adherence to dosing instructions.

“In my clinic for protease inhibitor failures, some patients who were never at risk for AIDS-related clinical events harbor virus strains that are resistant to all available drugs,” wrote Keith Henry, M.D., of Regions Hospital in St. Paul, MN in the February 15 *Annals of Internal Medicine*.

Rather than advising therapy when patients’ CD4 counts dip below 500, more specialists are following an individualized approach that puts off therapy. Recent revisions in the International AIDS Society-USA treatment guidelines reflect this new caution about the “hit hard, hit early” approach.

This issue of the amfAR Treatment Insider reports on two of the main discussions at the Conference on Retroviruses. One concerned residual HIV replication during HAART. A possible counter-strategy is the ironic use of therapy interruptions to mobilize anti-HIV immunity that would reinforce the drugs when reintroduced. The second discussion we take up here concerns antiviral therapy’s long-term metabolic effects, which may be reason enough for occasional drug holidays.

## Lacking a Knockout Punch, Medicine Hopes for a TKO

by Dave Gilden

Last November, Philadelphia researchers published the results of a small study they had done with their new gadget, an ultrasensitive plasma viral load analyzer that measures down to a mere five copies of HIV RNA per mL (*JAMA*; 282(27):1627-32). They looked at 22 patients in their clinics who had already tested below the usual 50 copies/mL cut-off for the ultrasensitive assay. The new ultra-ultrasensitive test found that all 22 had detectable viral loads. Their average was 17 copies/mL despite having been on successful HAART for as long as four and one half years.

"The present drugs are not potent enough to kill off all the virus. That's also true in other diseases, but there, the immune system cleans up the residual infection. Here, close is not good enough," commented Roger Pomerantz, M.D., the paper's senior author, who is from Thomas Jefferson University.

It may not be that everyone has some actively replicating HIV despite receiving therapy that heretofore seemed suppressive, but most seem to. Reports similar to the Philadelphia one have since cropped up in medical journals and the 7<sup>th</sup> Retrovirus Conference.

David Ho's group at the Aaron Diamond Research Center in New York reported in January (*Nature Medicine*; 6(1):82-5) that the slow decline in the numbers of cells containing quiescent, or latent, HIV is related to the frequency of transient "blips" in viral load. The group looked at 33 patients who had been on HAART for 13 to 36 months and generally kept their viral loads below 50. All but 12 had occasional transient peaks above the 50-copy/mL limit. The average number of these blips ranged from 0.4 to 5.8 per year. Those with the highest number of blips showed increases in the number of latently infected cells, considered HIV's final redoubt. (The current drugs cannot touch HIV that is not biologically active. The immune system itself has no way of finding and eliminating cells with completely quiescent HIV.)

A poster (#140) at the 7<sup>th</sup> Retrovirus Conference described testing 28 patients for the existence of the HIV RNA genome within their immune cells, the mark of virus in the process of reproducing. This RNA was found in every specimen from every patient, regardless of whether that patient experienced viral blips or not. The level of RNA, detected at an average of 277 copies per million white blood cells, was also independent of the length of time on HAART

even in those with no blips. The actual number of virus-producing cells was low, as each such cell contained about 1,000 copies of HIV RNA.

Those who are treated very early, during primary infection just after contracting HIV, fare little better than those treated later. A Swiss study (talk 210) presented at the 7<sup>th</sup> Retrovirus Conference found low levels of HIV-producing cells for up to two years after extreme viral suppression (plasma viral load below 3 copies/mL) in a cohort of 12 persons treated during primary infection.

This residual virus existing despite HAART might just represent a single round of replication originating in latently infected cells that become activated and produce HIV, which is then blocked by the antiviral drugs in a patient's system. That hopeful possibility was undermined by a study (talk 239) done by Tae-Wook Chun, M.D., who works with Tony Fauci at the National Institutes of Health. Dr. Chun and his associates examined nine persons who temporarily went off therapy, only to see their HIV population reach pretreatment levels within one to two months. When the NIH researchers examined the genetic makeup of this new population, they found that in seven out of nine cases, it exhibited marked differences from that found in latently infected cells.

### The Ordinary Infection Process Continues at Low Levels

If not from the latently infected cells, where does this replication come from? Another small study described at the 7<sup>th</sup> Retrovirus Conference (poster #136) sought to unravel that mystery. It studied the genetic variations in the HIV of 12 individuals. The newly formed virus arose in activated CD4 cells and monocytes and differed genetically from that found in the resting, latently infected CD4 cells. Those cells contained HIV that genetically looked like variants formed by activated cells in an earlier time period. The residual ongoing replication then contributes to the pool of latently infected cells rather than the other way around.

Continued replication provides the opportunity for further viral evolution. The implication of this danger was underscored at the Retrovirus Conference by Richard D'Aquila, M.D., of Harvard Medical School, who described an intensive genetic analysis of HIV clones isolated from patients with viral loads consistently below 50 copies/mL (talk 238). Five patients were on their second drug combination and were experiencing occasional viral load blips in the course of two years of therapy. All five had prior resistance-associated mutations, but all five also bore

evidence of additional mutations in at least some of the isolated HIV. In contrast, no new mutations could be detected in seven patients without viral load blips.

Detection of the drug resistance arising during successful HAART is everyone's great fear because it would indicate that HAART-induced suppression of HIV is inevitably limited in duration. Before reaching any conclusions, this study's many unresolved issues require resolution. For one thing, most of the mutations may have appeared in the early weeks of HAART, before HIV was maximally suppressed. The development of drug mutations might be due to a slower viral replication decay in certain patients.

Dr. D'Aquila's study at bottom is limited by the sensitivity of his assays, which makes it difficult to pinpoint when mutations associated with drug resistance first appear. It might just take longer for the patients without viral load blips to produce mutated HIV in detectable quantities. The appearance of additional drug resistance was charted in one patient after a mere one-week blip. That mutation may have already existed for some time, with its origin independent of any blip.

Dr. D'Aquila commented, "The take-home message is that there is still drug selection pressure on whatever little virus is still replicating. It is not the case that there is virus [in the body] with absolutely no exposure to the drugs." The patients, meanwhile, continue to do as well as before without changing therapy. The current mutations confer only slight resistance. The need for a preemptive alteration of their regimens is another of this study's open questions.

### **Treatment Interruptions: Employing the Immune System as Drug**

Michael Youle, M.B., of London's Royal Free Centre of HIV Medicine, notes, "In other therapeutic areas, for instance, oncology, rheumatology and infectious diseases, intermittent or cyclical therapy is the standard of care for some effective but highly toxic treatments. This approach is also clearly logical for symptomatic interventions or for relapsing and remitting conditions."

Three years ago, reports began circulating of the so-called Berlin patient, who erratically took a regimen of ddI/hydroxyurea/indinavir shortly after contracting HIV. He ultimately went off drugs entirely with little trace of residual virus. Since then, there has been growing attention paid to what has been called "drug holidays," "pulsed therapy" or, more recently, "structured treatment interruption" (STI).

Interest redoubled when it was realized that successful HAART treatment brought HIV levels so low that there was

not enough left to stimulate an anti-HIV immune response. What remained of that response in untreated people with HIV perversely declined after they commenced therapy (poster #582). The Retrovirus Conference contained reports of no fewer than 18 STI studies, all in very preliminary stages (see table). It was difficult to tell from this initial data whether the treatment pauses did any good. A common observation in these studies was that anti-HIV immune responses increased during STI. These were measured by tests of cell proliferation or interferon-gamma production among cells removed from patients and cultured in the lab along with HIV proteins.

In a Spanish study (latebreaker LB11), seven volunteers with viral loads less than 20 copies/mL on HAART went through three STIs in the course of the year. The first two lasted for four weeks but the third continued until viral load plateaued, after first peaking at much higher levels. In four of the seven, this equilibrium HIV level was 0.6 to 1.5 log (75 to 97%) less than pretreatment levels. All four had easily detectable plasma viral loads above 1,000 copies/mL. During the second and third interruptions, the extent of anti-HIV immune response by CD4+ T-helper cells and CD8+ cytotoxic lymphocytes (CTLs) correlated with lower viral loads at the end of the STI.

Bruce Walker, Eric Rosenberg and colleagues in Boston have been conducting a highly publicized STI study in seven individuals whose treatment began during primary HIV infection. According to a poster (#357) at the Retrovirus Conference, they have had results similar to the above-mentioned Spanish study. CTL responses to HIV greatly broadened and increased in frequency during the STIs. Three persons who have gone through two or three STIs maintained their viral loads around 5,000 copies/mL for eight to 17 weeks after an initial peak in HIV levels. All three decided to go back on therapy and try another STI later on, in an effort to reach a lower viral equilibrium.

Viral loads in the 1,000 to 10,000 range are not exceptional in persons with chronic HIV infection, and the Boston patients may have been properly cautious when they decided to recommence therapy. It is not that certain the observed increases in anti-HIV immunity will have any long-term protective effect. After all, such immune defenses frequently arise early in HIV infection, but ultimately fail, as the infection annihilates the CD4+ T-helper cells that orchestrate them. Indeed, the improvements in HIV immunity observed during STIs may not be newly created, just newly detected. The cells involved may have always been there. In treated patients (talk 458), there may not be

## Treatment Interruption Studies at the 7th Retrovirus Conference

Author	Abstract	No. of pts.	Stage of infection	Pre-STI VL BLQ?	Time off drugs	Results
Zala	558	8	Primary	Y	30 days	Pts received d4T/ddI/NVP± HU for >1 yr. VL peaked within 3 wks then dropped 80%.
Altfeld	357	7	Primary	Y	Until >5000 or pt request	Increased anti-HIV CTLs. 3 pts with 2-3 STIs had VL level off at 5-8,000 for 8-17 wks before restarting treatment.
Jin	LB12	4	Primary	Y	Up to 8 mos	HAART+ALVAC/gp160 vaccine, open-ended STI. 2 pts: strong anti-HIV CTLs and delayed rebound.
Kilby	359	5	Chronic	Y	8 days	3/5 had no detectable HIV during STI. In 1/5, an unplanned second stop led to primary HIV-like syndrome after 2 wks.
Orenstein	358	5	Chronic	Y	8 wks	Lymph node hyperplasia returns with viral load
Carcelain	356	3	Chronic	Y	1-3 wks/3-4 times	Emerging anti-HIV immune response (CD4 cells) destroyed by increased HIV replication.
Fagard	458	120	Chronic	Y	2 wks/4 times	SSITT trial - 96 pts through 1st STI, 23 through 3rd. No tendency yet for improved response with extra STIs.
Papasavvas	353	5	Chronic	Y	6-7 wks	Increases in anti-HIV CD4s and CTLs correlated with length of STI.
Garcia	LB11	10	Chronic	Y	2x until VL >200; 3rd until VL plateaus	7 pts through 3rd STI. 4 with lower viral load plateaus have new CD4 and CTL responses to HIV.
Stellbrink	240	12	Chronic	Y	~90 days	HAART± IL-2. Rapid rebound toward pretreatment VL. IL-2 made no appreciable difference in rebound rate.
Hatano	349	14	Chronic	Y	26-168 days	11/14 pts on HAART+ IL-2. Rebound to pre-HAART viral loads even after 3 yrs with VL <500.
Ruiz	354	12 (14 non-STI controls)	Chronic	Y	Until VL >3000 or 30 days every 2 mos	HAART± IL-2. 2 STIs in 5 pts: HIV detectable by day 21 both times. No new sustained CD4 response to HIV. IL-2 has made no appreciable difference so far.
Smith	355	9	Chronic	Y	>8 wks	Continued daily IL-2 after stopping HAART. VL plateau ~ 30,000. Open-ended STI.
Lori	352	17	Chronic	Y/N	8 wks	Case-matched comparison: 6/8 rebounded after stopping HAART, 0/9 after stopping ddi+ HU. (See article.)
Sherer	351	43	Primary /Chronic	N	>90 days	Retrospective study of unplanned interruptions of nucleoside analog regimens. 13 who maintained VL < 400 had very low pretreatment VLs.
Price	306	4	Chronic	N	12 wks	2/4 had disproportionate CSF VL rebound.
Deeks	LB10	17	Chronic	N	>12 wks	16/17 had switch from resistant to drug sensitive HIV after ~8.5 wks. Switch accompanied by VL up 6.6-fold and CD4 count down 94. 4/8 pts: Resistant HIV could still be cultured from cells when drugs are present.

Abbreviations: BLQ = below level of quantification (usually <50 copies/mL), CSF = cerebral spinal fluid, mos = months, pts = patients, VL = plasma viral load (in copies of HIV RNA/mL), SSITT = Spanish-Swiss Intermittent Treatment Trial, STI = structured treatment interruption, wks = weeks, yrs = years

Note: All of these trials are ongoing and will produce more data on further STIs. None have control arms except for the Ruiz trial. Where applicable, trial participants have had their HIV successfully resuppressed upon post-STI retreatment

enough HIV to activate them, In untreated ones (talk 186), the CD4 cells are unable to proliferate and defend the body in the face of chronically high levels of HIV. If they did manage to survive and control HIV, the virus would have mutated to escape the protective immune cells (*Nature Medicine* 5(11); 1270-6) just the way it manages to escape effective medications.

The one large STI trial presented at the Retrovirus Conference is just beginning to yield usable data. This trial is the 120-person Spanish-Swiss Intermittent Therapy Trial (poster #579). Its initial results are inconclusive. Only 30% of the 96 volunteers who have gone through the first two-week STI had no detectable rebound. So far, 54 persons have stopped therapy a second time and 23 a third time. During these subsequent STIs, there has been no clear tendency yet for HIV rebounds to decrease in frequency or amplitude.

The most successful report of the Retrovirus Conference STI studies involved an unconventional therapy – just ddI plus hydroxyurea for a period of over three years (poster #352). This combination of an antiviral and host cell modifier kept viral loads stable at an average 549 copies/mL among nine persons, only one of whom had a viral load below 50. The nine were matched with eight patients on HAART for two years, six of whom had viral loads below 50 (the other two were below 400). All 17 were taken off therapy for eight weeks. Treatment could resume earlier if viral loads went above 10,000 or CD4 counts dropped below 200.

By eight weeks, six of the eight HAART recipients had restarted therapy, but none of the hydroxyurea cohort had. As Franco Lori and the other authors of this report have noted before (6<sup>th</sup> Retrovirus Conference, 1999, poster #701), many of those in the hydroxyurea group had comparatively high anti-HIV immunity during their years of partially suppressed HIV. This may have made the difference.

Several caveats about this study are in order. The first is that the hydroxyurea cohort is a highly selected group. Its members come from a trial that originally followed 40 volunteers on ddI plus hydroxyurea for six months. The present cohort consists of those who decided to remain on the combination rather than seeking other regimens, protease inhibitor-containing ones in particular. These remaining volunteers may well have been in some way more successful or naturally more resistant to HIV than the others, though Dr. Lori says that there are no evident signs of this. Also, the hydroxyurea recipients were on their second STI while the comparison HAART group was on its first. Dr. Lori

concedes that at this point, we do not know how many people will benefit from a ddI/HU regimen that includes STIs or how long that benefit will last. More rigorous controlled trials with lengthy follow-up are necessary.

The results so far at least alleviated the fear that STIs would promote the rise of drug resistance. After all, if HIV is able to evolve slowly under HAART, that evolution might greatly accelerate in the HIV burst that occurs when treatment is removed. Patients might go off successful therapy and then fail to resuppress their HIV when they resume HAART – a nightmarish scenario.

None of the studies observed this phenomenon, at least so far. Everyone was able to go back on treatment and successfully resuppress their HIV to below 50 copies/mL, if that was their preinterruption level. These studies have lasted only a short time, though, and their treatment interruptions are tightly monitored and very conservatively structured.

One study (poster #358) did find another unfortunate occurrence: Researchers monitoring five volunteers found that after treatment ceases, lymph nodes quickly show signs of excess cell activation and start to degenerate in the manner typical of HIV infection. Previous reports have shown that lymph node architecture can recover during viral suppression. There also was reseeding of the latently infected cell pool. The five had been off therapy for one to two months and had seen their viral loads leap from under 50 copies/mL to 329 to 3.2 million. Before treatment was interrupted, their lymph nodes (examined by biopsy) had been nearly quiescent and close to normal in structure.

Surveying the STI reports at the Retrovirus Conference, Dr. Pomerantz commented, “The papers on STI are not very encouraging. Most people fail, but there’s enough that’s positive to keep on trying.” Research definitely will continue since all these studies are ongoing and will produce more extensive data covering more treatment interruptions. The final results may be no better than the current initial data. If so, other STI schedules – longer or more frequent breaks or more cycles on and off treatment, for example – could make a difference.

When HAART is successful, HIV is hit very hard indeed, decreasing by 99.9%, and HIV is clearly on the ropes. We then have some time to create the ideal knockout punch. Holding the line in the meantime seems like a TKO, and a practical strategy like STIs that promises to keep HIV in remission without endless medication is very appealing to most people.

## The Burden of Disease vs. the Burden of Treatment

by Dave Gilden

Even if treatment interruptions are not beneficial in terms of promoting the body's own immune defenses against HIV, they may have other uses. Keith Henry, who heads the HIV clinic at St. Paul, Minnesota's public hospital, echoed a common sentiment when he said, "Aggressive treatment looks good for six months, but continuous drugs might not be wise. We have unplanned treatment interruptions by the hundreds. I've given up worrying about them unless the therapy is endangered due to drug resistance. You may have to take breaks anyway, just to let the body recoup."

Another year has provided more information concerning the magnitude of long-term drug toxicities, and theories about their causes continue to multiply. The 7<sup>th</sup> Retrovirus Conference heard a number of reports on the incidence and mechanism of metabolic and physical changes related to fat processing.

The negative aspects of treatment are an increasingly attractive reason for taking a break. Still, there is no way of predicting at this point how much a break will reverse the accumulated side effects – or how much damage HIV will do at the same time.

### Whither Lipodystrophy?

"Lipodystrophy," first noticed in 1996, has always been a confusing topic. It is the rubric under which fall many of the physical and metabolic changes associated with HAART: elevated blood lipids, higher blood sugar and/or insulin, loss of subcutaneous fat (particularly in the limbs, buttocks and cheeks), breast enlargement, growth of fat pads between the shoulder blades ("buffalo hump"), and last but not least, increased deposits of fat around the organs in the abdomen ("protease paunch"). It has never been clear whether all these sometimes contradictory symptoms are due to the same mechanism, nor how prevalent they are.

Absence of common standards to evaluate the new abnormalities has made it difficult for researchers to compare their frequently contradictory data. At the 7<sup>th</sup> Retrovirus Conference, a number of large observational studies sought to better gauge the prevalence of the problem. Estimates of the frequency of changes in body fat ranged from 14.3% (poster #13) to about 67% (poster #14). An Australian survey (talk #201) of body fat abnormalities in

that country's HIV population recorded an overall prevalence of 54%, including 63% of those who had taken protease inhibitors and 32% of those with exposure to treatments that did not include PIs. Of those with no history of treatment, 21% showed some physical changes – mostly mild peripheral fat loss. The survey covered 1337 patients, nearly all men. Assessment was largely by physical exam and patient report, with a quarter of the cohort examined by DEXA, an x-ray scanning technique.

People who begin treatment during primary infection syndrome, which occurs just after contracting HIV, might be expected to escape some of the ravages wrought by the virus. They are not immune to disturbances in their fat processing and storage, though. A Spanish study (poster #12) followed 14 men and 3 women whose treatment started during primary infection. The 17 received a combination of d4T, 3TC and indinavir and were followed for a median of 20 months. Six of them (35%) developed some body-shape changes, with the percentage increasing as time went on. About half had high blood cholesterol and/or triglycerides. A recently published logical extension of this study followed 11 HIV-negative men on ritonavir for two weeks (*AIDS* 14(1):51-7). The men exhibited significant increases in their blood lipids – cholesterol and triglycerides – compared to eight controls who did not take ritonavir.

The general absence of women in many of these studies is frustrating because their pattern of fat metabolism differs from that of men. An update of the SALSA study (poster #26) a survey of 324 HIV+ American men and 71 HIV+ American women with body-shape abnormalities, was presented at the 7<sup>th</sup> Retrovirus Conference. Based on physicians' exam and patient self-report, SALSA found that the women tended to have more localized fat accumulation and less subcutaneous fat loss than the men. Elevations in blood cholesterol and triglycerides were one-third to one-half less frequent in the women. Only 63% of the women, compared to 81% of the men, had taken protease inhibitors.

Of course, the SALSA study does not give a picture of the overall frequency of these abnormalities, since it includes only people who already have them. Italian investigators presenting at the Retrovirus Conference (poster #28) reported that the two-year incidence of developing fat tissue aberration among women on protease inhibitors was about 45%, a figure similar to that for men.

Risk factors for developing the signs of lipodystrophy were similar in many of the studies. Generally, longer duration of HIV infection and treatment, lower

pretreatment CD4 count or percent, greater viral load drop, older age and elevated blood lipids or thicker fat layers when commencing treatment were predictors of one expression or another of lipodystrophy (poster #23). Among the drugs, indinavir and d4T were sometimes particularly implicated – and sometimes not.

White race also was sometimes associated with greater risk for lipodystrophy, which may explain the low-end 14.3% prevalence estimate mentioned above. That figure came from the Community Programs for Clinical Research on AIDS, which follows a population with more blacks and Hispanics than other studies.

### **Interacting Causes?**

The presence of signs of lipodystrophy in people who never took protease inhibitors has upset the original assumption that all the disturbances were inflicted by the protease inhibitors. These drugs may be the main actors, but nucleoside analogs and NNRTIs could be contributing to different aspects of the problem.

Protease inhibitors were supposedly designed to selectively bind to HIV's protease enzyme, but they may also bind to and disrupt some of the human molecules involved in removing lipids from the bloodstream and storing them as fat. James Lenhard, Ph.D., a project leader in GlaxoWellcome's diabetes/obesity unit, made a series of presentations on this subject at the 7<sup>th</sup> Retrovirus Conference. He found that the effect of the protease inhibitors varied in a specially bred strain of obesity-inclined, HIV- mice. Nelfinavir (poster #39), for example, increased triglycerides but not cholesterol in the mice's blood while indinavir (poster #38) heightened both. The effect of these protease inhibitors in cell culture reinforced the effects of other compounds known to alter retinoic acid signaling, which promotes the maintenance, proliferation, and maturation of fat cells.

If protease inhibitors are to blame for lipodystrophy, switching to a "protease-sparing" anti-HIV regimen might improve patients' symptoms. That was usually not apparent in the trials described at the Retrovirus Conference. A Spanish presentation (poster #206) described 48-week results for 108 volunteers who either switched to ddI/d4T/nevirapine or remained on their original d4T/3TC/protease inhibitor regimen. Here, cholesterol and triglyceride levels showed modest improvements with the change to the nevirapine regimen, but body-shape anomalies were no different between the two groups. The trial participants did report a significantly improved quality of life with nevirapine. HIV remained

suppressed in 90% of the nevirapine group and 94% of those who continued their PI.

The one study to find appreciable normalization of body-shape was a Glaxo Wellcome-sponsored study (poster #51) in 211 people, 106 of whom exchanged their protease inhibitor for the Glaxo's nucleoside analog abacavir. The group as a whole started with borderline high blood lipids. Cholesterol levels declined substantially over 24 weeks among those receiving abacavir. In a substudy of just 18 persons with lipodystrophy, three of nine reported improvements in their body-shape while one reported a worsening. All nine remaining on protease inhibitors had worse signs of lipodystrophy at the end of the 24 weeks. Abdominal girth and breast size in particular seemed to decrease in the abacavir group.

One of the reasons that these protease inhibitor discontinuation trials did not have impressive results is that the nucleoside analogs themselves can affect fat metabolism. d4T has received particular blame for this, although several studies (for example, poster #21) at the 7<sup>th</sup> Retrovirus Conference did not find a particular association with this nucleoside analog. One trial, conducted by Thierry Saint-Marc of Lyon, France, did find that switching from d4T to abacavir, AZT or AZT/3TC reversed some signs of lipodystrophy. Forty-one of his patients were also on protease inhibitors, and 18 originally were receiving just d4T and a second nucleoside analog (ddI or 3TC). After 12 months, 29 of the PI-takers and 15 of those on dual nucleoside analogs had major improvements in subcutaneous fat, both in the limbs and the abdomen. Triglycerides also declined, but other parameters, including visceral fat and cholesterol remained unchanged.

Whether or not d4T is a particular culprit, the Saint-Marc study jibes with the growing feeling (symposium lecture #S21) that nucleoside analogs play some part in the overall long-term toxicity picture. It has been known ever since the introduction of AZT that nucleoside analogs interfere with the functioning of the mitochondria, the cell components that produce energy by means of oxidation. The mitochondria contain some of their own genes, which are duplicated when a mitochondrion replicates within a cell. The enzyme that duplicates the mitochondrial DNA is more primitive than its analog in the cell nucleus. Like HIV's reverse transcriptase, the mitochondrial enzyme's activities are interrupted by AZT, ddI and the rest of the nucleoside analogs.

Most of the side effects of nucleoside analogs, including neuropathy, myopathy (muscle wasting),

pancreatitis, suppression of white blood cell production in the bone marrow and high lactic acid levels in the blood are thought to arise from mitochondrial dysfunction. If some of the nucleoside analogs affected the mitochondria in fat tissue, it might show up as loss of ability to remove lipids from the bloodstream and create fat. Abnormal fat deposits might then build up in tissues less affected by nucleoside analogs. Similar fat redistribution occurs in Madelung's disease, a condition unrelated to HIV that is known to result from mitochondrial dysfunction.

There is another reason why the protease inhibitor- to-NNRTI switching studies failed to demonstrate conclusive results. Three of them utilized efavirenz as the NNRTI. It has been noted before (7<sup>th</sup> Euro. Conf. on Clinical Aspects and Treatment of HIV, Oct. 1999, talk #112) that efavirenz tends to raise blood lipid levels. Glaxo's James Lenhard observed that efavirenz raised triglyceride and cholesterol levels in the blood and caused liver enlargement in his mouse model (poster #41). Dr. Lenhard discovered that efavirenz, at least at high doses, decreased the mouse liver's production of enzymes that participate in fat oxidation. This impairment would reinforce the mitochondrial damage caused by nucleoside analogs. High dose efavirenz also had the effect of increasing lipid-synthesizing enzymes in subcutaneous fat cells.

## Little Contribution to Mortality – Yet

A University of Wisconsin group reported at the 7<sup>th</sup> Retrovirus Conference on their observations of impaired arterial wall flexibility in people taking protease inhibitors (poster 29). Twenty-one HIV+ patients receiving protease inhibitors were compared to seven on non-PI regimens. As measured by ultrasound imaging, flow-mediated arterial expansion was much lower in the protease inhibitor receivers. Combined with the PI group's higher blood lipids, the decreased ability of arterial walls to expand increases these individuals' risk of heart attacks. Their arteries would be less able to compensate for blood clotting arising after rupture of fatty plaques on arterial walls.

Six studies, though, found no evidence of increased frequency of cardiovascular disease in persons on protease inhibitors, whether by checking hospital records or using ultrasound to measure artery wall thickness. Observation times were very limited, to less than 30 months of PI treatment, which is probably not long enough for heart disease to express itself. The four ultrasound studies did find increased fatty plaques on artery walls of people with HIV compared to their HIV-negative counterparts (poster #30) an observation that may become accentuated as the high lipid levels associated with protease inhibitors continues over the years.

The largest of the cardiovascular disease studies (poster #33) checked the records of 4500 HIV+ members of the huge HMO Kaiser Permanente Northern California. From January 1996 to June 1999, there was no significant difference in coronary heart disease incidence among all patients with HIV, those receiving protease inhibitors and Kaiser's general membership.

People are still dying from HIV-associated causes, but the long-term side effects of antiretroviral drugs have yet to show themselves in the mortality figures. At the 7<sup>th</sup> Retrovirus Conference, eight posters looked at mortality statistics. A Seattle survey (poster #464) of 724 persons with AIDS found that treatment with HAART reduced the risk of dying by 60%. A French cohort (poster #461) presented the most extensive and complete results. In its 1143 HIV clinic patients, the death rate declined 75% since the introduction of HAART but was still 9.5 times that of the general population.

Causes of death mentioned in these reports are mainly the traditional opportunistic infections plus a growing number of "pre-AIDS" conditions that can also affect HIV-negative persons, usually to a lesser extent. These include hepatitis C, septicemia (blood-borne infections that occur especially among IV drug users), pneumonia and malignancies (including lung cancer).

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