

# BETA

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***Making the Decision  
to Start Therapy***

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***ADAP in Peril***





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notice

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NEWS  
BRIEFS

Liz Highleyman

**For the latest updated guidelines for HIV treatment in adults, adolescents, children, and pregnant women; postexposure prophylaxis (PEP) for occupational and non-occupational exposure; and opportunistic illness (OI) prevention, visit [www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov).**

## REPORTS FROM THE 11<sup>TH</sup> RETROVIRUS CONFERENCE

Nearly 4,000 participants gathered February 8-11, 2004, for the 11<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, the major annual U.S. scientific meeting on HIV. The conference opened with Stephen Lewis, United Nations Special Envoy for HIV/AIDS in Africa, calling on the developed world to devote more funding to AIDS relief efforts in poor countries. Some new epidemiological information was presented—including a report of an unexpected HIV outbreak among college men in North Carolina—but the Retrovirus conference was primarily devoted to basic science and treatment.

For the 2004 Retrovirus conference program and abstracts, see [www.retroconference.org](http://www.retroconference.org).

For more complete conference coverage, see:  
[www.hivandhepatitis.com/2004icr/11croi/main.html](http://www.hivandhepatitis.com/2004icr/11croi/main.html)  
[www.thebody.com/confs/retro2004/retro2004.html](http://www.thebody.com/confs/retro2004/retro2004.html)  
[www.natap.org/2004/CROI/croi.htm](http://www.natap.org/2004/CROI/croi.htm).

### ***Nevirapine Resistance after a Single Dose***

HIV can develop resistance to nevirapine (Viramune) after just one dose, which has important implications for the use of single-dose nevirapine monotherapy to prevent mother-to-child HIV transmission in resource-poor settings.

Gonzague Jourdain, MD, from Harvard School of Public Health (abstract 41LB) reported results from a Thai study of more than 1,800 HIV positive pregnant women who received AZT (zidovudine, Retrovir) with or without single-dose nevirapine. Women and infants who received the combined regimen had a vertical transmission rate of just 2%, comparable to rates seen in the U.S. and Europe. Following delivery, about 25% of the women began taking triple-drug regimens containing nevirapine. A random subset of 90 women received genotypic resistance tests 10 days after giving birth; resistance mutations (e.g., K103N, Y181C, G190A) were detectable in 18%. After six months of treatment, only 34% of women who had taken nevirapine monotherapy during delivery and had resistance mutations had viral loads below 50 copies/mL, compared with 53% of women who had taken intrapartum nevirapine but did not have resistance mutations, and 75% who did not receive nevirapine during delivery. In a second study of more than 600 HIV positive mothers in South Africa, presented by Neil Martinson from Johannesburg (abstract 38), about 39% of HIV positive mothers and about 42% of infants who were infected despite use of nevirapine developed resistance to the drug.

HIV easily develops cross-resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs), and nevirapine resistance can also limit future use of efavirenz (Sustiva) and possibly other NNRTIs yet to be developed. Some research suggests that nevirapine resistance may be short-lived. In the Thai study, mothers who started a nevirapine-based regimen more than six months after delivery responded better than those who started therapy sooner; however, in the South African study, nevirapine-resistant HIV persisted for at least nine months. Because the single-dose nevirapine regimen is inexpensive, convenient, and effective in reducing mother-to-child transmission, experts are not calling for an end to its use in areas with limited resources. “Single-drug therapy should not be withheld if no other alternative exists,” said Elaine Abrams, MD, from Columbia University in the session’s concluding remarks. Wherever possible, however, HIV positive pregnant women should receive combination antiretroviral therapy as appropriate for their viral load and CD4 cell count.

### ***Atazanavir Still Looks Good at 48 Weeks***

Following up on 24-week data presented at last summer’s International AIDS Society meeting showing that atazanavir (Reyataz) boosted with ritonavir (Norvir) is nearly as effective as lopinavir/ritonavir (Kaletra), Margaret Johnson, MD, from the Royal Free Hospital in London (abstract 547) reported that boosted atazanavir continued to suppress HIV at 48 weeks. The BMS 045 study included 358 treatment-experienced participants with resistant virus randomly assigned to receive boosted atazanavir, atazanavir plus saquinavir (Invirase or Fortovase), or lopinavir, along with tenofovir DF (Viread)

plus a nucleoside reverse transcriptase inhibitor (NRTI). After 48 weeks, 46% of subjects receiving lopinavir had viral loads below 50 copies/mL, compared with 38% receiving boosted atazanavir and 26% receiving atazanavir/saquinavir. Participants in the boosted atazanavir and lopinavir/atazanavir arms had CD4 cell increases of about 115 cells/mm<sup>3</sup>, while the third arm saw a gain of 72 cells/mm<sup>3</sup>. While lopinavir appears slightly more effective, atazanavir is less likely to cause gastrointestinal problems or blood lipid (fat) abnormalities.

In related news, recent small studies have shown that atazanavir can be used to boost blood levels of amprenavir (Agenerase) and saquinavir—a potential benefit for individuals who cannot tolerate ritonavir. Also, a case report series published in the April 9, 2004 issue of *AIDS* suggests that beyond causing fewer lipid abnormalities itself, atazanavir may help reverse dyslipidemia (blood lipid abnormalities) and lipodystrophy (body shape changes) associated with use of other protease inhibitors (PIs). Within 12 weeks of switching to atazanavir, two individuals experienced reduced dorsocervical fat pad (“buffalo hump”) size and one experienced decreased waist size; lipid levels declined in all three, and the subjects maintained viral loads below 50 copies/mL. “We propose that in patients with lipodystrophy syndrome, switching to atazanavir from established [PIs] could lead to a reversal of the metabolic alterations and...rapid regression of pre-existing body fat accumulations,” the authors concluded.

### Treatment During Acute Infection

There appears to be little benefit to starting antiretroviral therapy in the months immediately following HIV infection, according to a presentation by Bruce Walker, MD, from Harvard Medical School (abstract 24). Walker presented final data from a small cohort of individuals who began therapy during acute, or primary HIV infection (PHI) followed by supervised treatment interruptions (STIs). Researchers have hypothesized that such interruptions might help spur the immune system to fight HIV. Earlier data from the study looked promising, with all eight initial subjects demonstrating continued viral suppression after one or two STIs. (Subjects were restarted on therapy if their viral loads stayed above 5,000 copies/mL for three weeks, or ever increased above 50,000 copies/mL.) With 14 subjects now enrolled and after an average of five years of follow-up, however, it appears that the ability to control HIV without treatment is short-lived. While 11 subjects maintained virological control for at least 90 days, that figure dropped to six subjects after one year, and to three subjects after three years. Most participants experienced gradual increases in viral load and declines in CD4 cell count. HIV-specific CD8 cell responses increased three-fold during the first STI, less during the second and third interruptions, and not at all after subsequent breaks; however, increased CD8 response did not correlate with improved virological control. In addition, two reports

based on data from the French PRIMO study (abstracts 396 and 397) also failed to demonstrate benefits from early therapy and STIs. In an editorial review in the March 26, 2004 issue of *AIDS*, Walker and coauthors concluded, “Based on the currently published data, there is no clear evidence that patients with access to antiretroviral therapy have any greater clinical benefit if therapy is introduced immediately during or prior to their seroconversion illness...[T]here is currently no evidence from these studies to suggest that therapy during PHI results in a reduction in clinical progression compared with use of effective therapy in later disease.”

### Promising HIV/HCV Coinfection Data

Coinfection with HIV and hepatitis C virus (HCV) received considerable attention at the Retrovirus conference. Douglas Dieterich, MD, from Mt. Sinai School of Medicine presented eagerly awaited results from the Roche APRICOT study of 868 coinfecting subjects in 19 countries (abstract 112). Participants were randomly assigned to receive standard interferon plus ribavirin, Pegasys brand pegylated interferon plus placebo, or Pegasys plus ribavirin, all for 48 weeks. Most participants were white men on HAART with well-controlled HIV. Overall, 40% of the participants treated with Pegasys/ribavirin achieved a sustained virological response (SVR; undetectable HCV viral load at the end of a 24-week post-treatment follow-up period)—the highest SVR rate yet seen in a coinfecting population—compared with just 12% of those receiving standard interferon/ribavirin. Among those with genotype 1 HCV (which is harder to treat), the corresponding SVR rates were 29% and 7%; among those with genotypes 2 or 3, the SVR rates were 62% and 20%, respectively.

At the same session, Raymond Chung, MD, from Massachusetts General Hospital (MGH) presented final results from ACTG A5071 (abstract 110). In this trial, 133 participants received either standard interferon or Pegasys for 48 weeks; both groups also received daily ribavirin, starting with lower than normal doses to reduce side effects. Most participants were men and about half were African American. After 72 weeks (48 weeks of therapy plus 24 weeks of follow-up), 27% in the Pegasys/ribavirin arm and 12% in the standard interferon/ribavirin arm had undetectable HCV viral load. Among those with genotype 1, the corresponding SVR rates were 14% and 6%; among those with genotypes 2 or 3, the SVR rates were 73% and 33%, respectively. Notably, while the end-of-treatment and SVR rates were similar in the standard interferon arm, the response rate declined dramatically from week 48 to week 72 in the Pegasys arm. Chung suggested that the lower initial dose of ribavirin may have contributed to the higher relapse rate.

Finally, Christian Perronne, MD, presented results from the French RIBAVIC trial (abstract 117LB). This study compared Peg-Intron brand pegylated interferon to standard interferon, both with ribavirin. Most participants

were men and 40% had advanced liver disease. Overall, 27% of participants receiving Peg-Intron/ribavirin had sustained undetectable HCV viral load after 72 weeks, compared with 19% of those taking standard interferon/ribavirin. Among those with genotype 1 HCV, the SVR rates were 15% and 5%; in those with genotypes 2 or 3, the corresponding rates were 45% and 40%. About 40% of subjects in both groups stopped treatment prematurely, and about 30% experienced severe side effects.

It is unclear why the SVR rates were so much higher in APRICOT compared with the other two trials, but there were some important differences in the study populations. Subjects in all three trials had well controlled HIV with median CD4 cell counts of 400–500 cells/mm<sup>3</sup>; at least 80% were on HAART. However, ACTG 5071 included more African Americans, a group that responds less well to interferon therapy. RIBAVIC included more participants with advanced liver disease, another “hard to treat” population, and drop-out rates were higher than in the other two trials.

### **Efavirenz Side Effects in People of Color**

Data from substudy A5097s of the ACTG 5095 trial presented by Heather Ribaldo of Harvard School of Public Health (abstract 132) revealed that people of color clear efavirenz more slowly than whites. The substudy included about 200 participants (53% white, 32% black, 12% Hispanic); about 80% were men. Black and Hispanic subjects cleared the drug about 30% slower than whites. Similarly, Stephen Taylor, MD, from the University of Birmingham in the U.K. (abstract 131) presented data from the STOP study showing that efavirenz reaches higher concentrations and persists longer after drug discontinuation in black women compared with white men.

Helping to explain this effect, David Haas of Vanderbilt University (abstract 133) reported data from another ACTG 5095 substudy showing that a gene variant seen most often in blacks is associated with slower efavirenz clearance and thus higher drug concentrations in the body. The gene controls expression of the CYP2B6 enzyme in the liver, which plays a role in drug processing. Each individual has one of three genotypes: T/T, G/T, or G/G. The T/T genotype (indicating two copies of the variant gene) was seen in 20% of blacks and just 3% of whites. Efavirenz concentrations were nearly three times as high in people with the T/T genotype, and slightly higher in those with the G/T combination, than in those with the G/G pairing. In this study, the T/T genotype was associated with adverse central nervous system side effects (e.g., bizarre dreams, depression). In related news, Lucia Gallego and colleagues from Madrid reported in the February 1, 2004 issue of *Clinical Infectious Diseases* that higher blood concentrations of efavirenz are associated with sleep disturbances such as insomnia and waking during the night. Together, these studies suggest that therapeutic drug monitoring may help physicians determine appropriate individualized levels of efavirenz.

### **Treatment Complications**

Metabolic side effects associated with HAART remain a major cause for concern, but studies of long-term complications continue to yield frustratingly inconsistent data. On the cardiovascular front, the latest analysis of data from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) trial, collected from more than 23,000 HIV positive individuals, revealed a cardiovascular event rate of 5.5 per 1,000 person years (PY), including 121 heart attacks and 30 strokes (abstract 737). The heart attack rate among subjects on HAART was only slightly higher than that seen in the Framingham Heart Study, a long-term study of cardiovascular risk factors in the HIV negative population. However, risk increased with longer duration of antiretroviral therapy. In the D:A:D study, HAART was not associated with hypertension (high blood pressure) (abstract 75), but in the Women’s Interagency HIV Study (WIHS) use of HAART—and increased duration of therapy—were independently associated with new-onset hypertension (abstract 741). Uchenna Iloeje, MD, from Bristol-Myers Squibb (abstract 736) reported that in a subset of the HIV Outpatient Study (HOPS) cohort, PI use was associated with an increased risk of cardiovascular disease (9.8 per 1,000 PY in the PI group vs 6.5 per 1,000 PY in the non-PI group), along with traditional risk factors such as older age, tobacco use, hypertension, and hyperlipidemia (elevated blood lipids). With PIs looking problematic, it is reassuring that T-20 (enfuvirtide, Fuzeon) was not associated with metabolic abnormalities or body fat changes after 48 weeks (abstract 715); this is not surprising, since T-20 works by a different mechanism than other antiretroviral drugs and does not interfere as much with normal cellular functioning.

Todd Brown, MD, from Johns Hopkins (abstract 73) presented data from the ongoing prospective MACS study showing that HIV positive men using HAART had higher rates of hyperglycemia (high blood sugar; fasting glucose 110 mg/dL or higher) and diabetes (fasting glucose 126 mg/dL or higher) compared with HIV negative men. The study included 5,622 gay or bisexual men, about 85% white. Overall, the risk of prevalent (existing) and incident (new onset) fasting hyperglycemia was 2–3 times greater, and the risk of prevalent and incident diabetes was 4–5 times greater, in HIV positive men on HAART compared with HIV negative men. In an incidence analysis of 765 subjects (after excluding those with hyperglycemia at study entry), about 19% of HIV positive men on HAART developed new-onset hyperglycemia, compared with about 9% of HIV positive men not on HAART, and about 11% of HIV negative men; the corresponding incidence rates for frank diabetes were about 11%, 5%, and 3%. Use of any PI, d4T (stavudine, Zerit), or efavirenz was associated with an increased risk of hyperglycemia. In addition, men with lower nadir (lowest ever) CD4 cell counts were more likely to develop blood glucose abnormalities.

## Deaths Due to Non-AIDS-Defining Illnesses

With HAART causing dramatically lower rates of opportunistic illnesses (OIs), an increasing proportion of deaths in people with HIV are now due to non-AIDS-defining illnesses. Frank Palella, MD, of Northwestern University (abstract 872) presented the latest analysis of data from the HOPS cohort, showing that while the rate of death due to OIs fell from 23 per 100 PY in 1996 to 6 per 100 PY in 2002, mortality due to nonopportunistic causes rose during the same period by 45% among individuals on HAART for two years, and by 70% among those on HAART for seven years. "If someone takes [antiretroviral therapy], they will live longer and when death occurs, it will not be due to an AIDS-related condition," Palella concluded.

One area where this shift is evident is the increased rate of nonopportunistic cancers in people with HIV. AIDS-defining malignancies such as Kaposi's sarcoma (KS) and invasive cervical cancer have declined in the HAART era. For example, in the May 10, 2004 online edition of *Cancer*, researchers with the EuroSIDA trial reported that in a study of nearly 10,000 HIV positive subjects, the rate of KS declined 39% from 1994 to 2003; the decrease was especially marked in participants with higher CD4 cell counts and those with a longer duration of HAART use. But rates of some other types of cancer are on the rise. Based on a retrospective analysis of data from more than 12,000 HOPS participants collected between 1992 and 2000, Pragna Patel, PhD, from the Centers for Disease Control and Prevention (CDC) (abstract 81) found that rates of lung, head/neck, and anorectal cancer, Hodgkin's lymphoma, and malignant melanoma were higher in people with HIV than in the general population. The incidence of other common cancers (e.g., breast, colon, prostate) was not significantly different in the HIV positive and HIV negative populations. The likelihood of developing a nonopportunistic cancer was correlated with nadir CD4 cell count. This suggests that immune suppression plays a role in the development of cancer, for example by allowing oncogenic (cancer-causing) viruses such as human papillomavirus (HPV) and Epstein-Barr virus (EBV) to proliferate.

## Back to the Drawing Board for HIV Vaccines

After several HIV vaccine studies have shown little or no benefit, Ronald Desrosiers, MD, from Harvard Medical School (presentation 109) suggested that it might be time to go back to the laboratory to learn more about how the immune system responds to the virus. According to Desrosiers, none of the dozen or so current HIV vaccine candidates have much likelihood of success, due to the present "inability to solve some fundamental scientific questions." At the same session, Dennis Burton, MD, from the Scripps Research Institute (presentation 108) said that the standard vaccine strategy of mimicking the human immune system—for example, encouraging heightened immune cell activity and/or antibody production—is not

the best approach, since the immune system itself is not very good at controlling HIV. Desrosiers suggested that more research on basic immunology is indicated before spending more time and money on large human trials of current vaccine candidates.

## Superinfection Rate 5%

In a small study of men who have sex with men in San Diego and Los Angeles, researchers observed an HIV superinfection rate of 5% per year, higher than previously assumed. (Superinfection refers to subsequent infection with a new strain of the virus in a person who is already HIV positive.) Davey Smith, MD, from the University of California at San Diego (UCSD) (abstract 21) detected three cases of superinfection out of a total of 78 men by matching HIV *pol* gene sequences. All three men were exposed to their second strain through sexual activity. None were on antiretroviral therapy; two men were initially infected with drug-resistant strains and then superinfected with a wild-type (nonmutated) strain, while the third was superinfected with drug-resistant virus. Studies have shown that infection with more than one strain of HIV can lead to more rapid disease progression; indeed, in this study the men experienced viral load increases and CD4 cell decreases after becoming superinfected. The results suggest that even two individuals who are already HIV positive should consider safer-sex precautions.

## More Conference News in Brief

Michael Kozal, MD, from Yale University (abstract 35LB) reported that a small proportion of HIV positive men who have sex with men (about 7% in his study) may be responsible for a large proportion of sexual transmissions. Peter Chin-Hong, MD, from the University of California at San Francisco (UCSF) (abstract 845) reported that individuals with drug-resistant HIV were at least as likely as those with susceptible virus to have unprotected sex; factors associated with unprotected sex included younger age, less education, use of sildenafil (Viagra), and depression. John Mellors, MD, from the University of Pittsburgh (abstract 39) reported that low-level resistance due to "minority variants" (those that comprise less than 25% or so of the HIV in the body) may not be detected by standard genotypic resistance tests. Finally, Cheryl Jay, MD, from UCSF (abstract 496) reported results from a small study showing that smoked marijuana relieves pain due to peripheral neuropathy, a possible side effect of certain NRTIs. After smoking three marijuana cigarettes per day for seven days, 10 out of 16 subjects reported that their average daily neuropathy pain decreased by 30% or more.

## SCULPTRA RECOMMENDED FOR FACIAL WASTING

A Food and Drug Administration (FDA) advisory group voted unanimously on March 25 to recommend conditional

approval of a new treatment for facial wasting (lipoatrophy) in people with HIV. Sculptra, manufactured by the French company Aventis and marketed by Dermik Laboratories, is an injected substance (polylactic acid) that causes the body to produce collagen (a fibrous protein) to fill in areas of lost fat. Results from studies to date (mostly in white men) have been impressive, with most treated individuals reporting a high degree of satisfaction. The therapy is not permanent, however, and repeated injections may be needed. Common side effects include pain at the injection site, temporary bruising, swelling, and small nodules (lumps) under the skin. To reduce the risk of adverse outcomes, Sculptra should be administered only by trained practitioners. Polylactic acid—under the name New-Fill—has been approved in Europe since 1999 for cosmetic use. The pending U.S. approval would be only for HIV-related facial fat loss; advisory panel members expressed concern that once approved, Sculptra could be used off-label for other cosmetic purposes such as reducing wrinkles.

## RAPID ORAL HIV TEST APPROVED

Also in late March the FDA approved the first rapid oral HIV antibody test. The new version of the OraQuick test, manufactured by OraSure Technologies of Bethlehem, PA, uses a sample of oral fluid taken with a swab from around the gums. Results can be read in about 20 minutes. The rapid OraQuick test was previously approved only for use with blood samples. The new test is more than 99% accurate; a positive result should be confirmed with a Western blot test. The rapid oral test will allow individuals to receive their results during a single session. When using older antibody tests, many people never returned to obtain their results, which typically took about two weeks. The test, expected to cost \$12 to \$15, will be available at some 40,000 approved medical laboratories, and federal officials have approved a waiver to use the test in other settings such as doctors offices, community clinics, and mobile vans. The rapid oral HIV test is not approved for home use.

## GENERIC RIBAVIRIN

In welcome news for the 30-40% of HIV positive people coinfecting with HCV, the FDA in early April approved two generic versions of ribavirin, an antiretroviral drug used in combination with standard or pegylated interferon to treat chronic hepatitis C. The generic drugs will be marketed by Sandoz (a subsidiary of Novartis) and Three Rivers Pharmaceuticals in partnership with Pharmaceutical Resources, Inc. Patient advocates have long called for the approval of generic ribavirin, which has been held up for years by patent lawsuits. But many were disappointed at the announced cost of the new versions. Generic drugs are typically priced at a fraction of the cost of their brand-name equivalents. Both Sandoz and Three Rivers, however, set prices for their generic ribavirin at about \$10 per capsule—in between the average wholesale prices for

Schering-Plough's Rebetol (about \$11) and Roche's Copegus (about \$6). Schering countered by announcing its own generic version of ribavirin, priced to undercut the two newcomers. The first manufacturer(s) of new generic drugs receive exclusive marketing rights for six months, but more companies are expected to enter the generic ribavirin market by the end of the year, thus driving down prices.

## T-1249 DEVELOPMENT HALTED

As mentioned briefly in the Winter 2004 edition of *BETA*, Roche and Trimeris announced in January that they have halted clinical trials of T-1249, a fusion inhibitor that was touted as a more potent second-generation successor to T-20. Like T-20, T-1249 must be administered by injection. The two companies said they remain committed to developing new fusion inhibitors that are more effective and easier to administer—a process expected to take years, according to David Reddy, PhD, Roche's head of HIV research. T-1249 (again like T-20) is a peptide that has proven difficult to manufacture; Roche said it was not confident it could produce T-1249 on a large scale. Advocates speculate that Roche abandoned T-1249 in part because sales of T-20 have not met expectations, largely due to its inconvenient twice-daily administration and exceedingly high price (about \$20,000 per year).

In related news, Roche announced that as of late April, T-20 would be available through retail and specialty pharmacies. Previously, due to supply limitations, the drug had to be ordered through a single mail-order distributor. Roche also said it plans to launch a nursing support program to assist individuals in preparing and administering the drug. Finally, a new set of international consensus guidelines for the use of T-20 were published in the May 21, 2004 issue of *AIDS*. The consensus panel said that successful treatment is most likely if T-20 is started when the CD4 cell count is above 100 cells/mm<sup>3</sup> and is used as part of a third or fourth regimen in conjunction with one or two other drugs to which HIV remains sensitive. But T-20 may also benefit heavily treatment-experienced individuals, including those taking few or no other active drugs.

## NEW NEVIRAPINE WARNING

In late January Boehringer Ingelheim issued a "Dear Doctor" letter warning of the risk of hepatotoxicity (liver toxicity) associated with the use of nevirapine (Viramune). "Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis [tissue death] and hepatic failure, has been reported in patients treated with Viramune," reads the company's revised package insert. Studies have shown that the risk of liver damage is about three times higher in women (including pregnant women) than in men. The risk of hepatotoxicity is especially high in women with more than 250 CD4 cells/mm<sup>3</sup> and men with more than 400 cells/mm<sup>3</sup>. People with existing elevated liver enzyme (ALT and AST) levels and those coinfecting with hepatitis B

or C are also at higher risk. Although the absolute risk of severe hepatotoxicity is small, the insert states that “patients with signs or symptoms of hepatitis must discontinue Viramune and seek medical evaluation immediately”; such symptoms may include fatigue, loss of appetite, nausea, abdominal pain, and jaundice. “It is essential that patients be monitored intensively during the first 18 weeks of therapy with Viramune to detect potentially life-threatening hepatotoxicity or skin reactions,” the company advises. If these adverse events occur, *the drug should not be restarted*. Complete nevirapine prescribing information is available at [www.viramune.com](http://www.viramune.com).

## UPDATED HIV TREATMENT GUIDELINES

On March 23 the U.S. Department of Health and Human Services (DHHS) again updated its guidelines for the treatment of adults and adolescents with HIV. For treatment-naïve individuals, the newly approved protease inhibitor fosamprenavir (Lexiva)—with or without ritonavir—has been added as a component of alternative PI-based regimens, while the older, less potent amprenavir has been removed. Unboosted indinavir (Crixivan) has also been removed as a component of initial regimens. Abacavir (Ziagen) plus 3TC (lamivudine, Epivir) has been added as an alternative double-NRTI backbone. In terms of safety, new information has been added regarding nevirapine-associated hepatotoxicity (see “New Nevirapine Warning,” above), as well as a new table of dosing recommendations for individuals with liver or kidney dysfunction. The federal government’s guidelines for the use of antiretroviral agents in children with HIV were also recently updated to include information on fosamprenavir. The revised adult and pediatric guidelines are available at [www.aidsinfo.nih.gov/guidelines](http://www.aidsinfo.nih.gov/guidelines).

## BEST INITIAL REGIMEN

The DHHS guidelines list a variety of preferred and alternative antiretroviral regimens for first-line therapy, but recent reports suggest that one initial three-drug combination is superior to its competitors.

Two articles in the December 11, 2003 issue of the *New England Journal of Medicine (NEJM)* reported data from ACTG study 384, the most extensive head-to-head comparison of consecutive regimens to date. The study included 980 treatment-naïve participants in the U.S. and Italy (approximately 80% men and 45% white) randomized to receive one of six different three- or four-drug combinations:

AZT	+ 3TC	+ efavirenz	
AZT	+ 3TC	+ nelfinavir	
d4T	+ ddi	+ efavirenz	
d4T	+ ddi	+ nelfinavir	
AZT	+ 3TC	+ efavirenz	+ nelfinavir
d4T	+ ddi	+ efavirenz	+ nelfinavir

Subjects in the three-drug arms were switched to a new regimen if they experienced virological failure or

discontinued due to toxicity; the primary study endpoint was length of time until failure of the second regimen. Participants were followed for a median of 2.3 years.

Gregory Robbins, MD, of Harvard Medical School and colleagues found that among the 620 subjects started on a three-drug regimen, initial use of AZT/3TC/efavirenz produced the most durable HIV suppression. At the end of follow-up, 90% of subjects who started with this regimen still had undetectable viral loads, compared with 60-70% of subjects who started with one of the other three-drug regimens. Robert Shafer, MD, of Stanford University Medical Center and colleagues compared the same 620 subjects with an additional 360 participants who received both efavirenz and nelfinavir plus either AZT/3TC or d4T/ddI. The four-drug regimens suppressed HIV longer than any of the three-drug regimens except AZT/3TC/efavirenz, which was comparable. As has come to be expected, the d4T/ddI backbone was associated with higher rates of adverse side effects than AZT/3TC. In an editorial in the same issue, Paul Skolnik, MD, of Boston University said that the results do not show that NNRTI-based regimens are necessarily better than PI-based regimens for first-line therapy, but starting with AZT/3TC/efavirenz allows the generally more potent PI class to be saved for future use.

While physicians and people with HIV are eager to adopt simpler regimens, there are risks in making things too simple. In the April 29, 2004 issue of *NEJM* Roy Gulick, MD, and colleagues from the ACTG A5095 study team reported that the triple-NRTI regimen of AZT, 3TC, and abacavir (the three drugs in the Trizivir combination pill) was inferior to regimens containing AZT, 3TC, and efavirenz, with or without abacavir. In this study of 1,147 subjects, 21% of those taking AZT/3TC/abacavir and 11% of those taking the efavirenz-based regimens experienced virological failure after a median follow-up of 32 weeks. (The difference was so great that the triple-NRTI arm was suspended following an interim review of the data.) This trial and others suggest that once-daily NRTI-only regimens may not be sufficiently potent to keep HIV under control for most people (see “News Briefs,” *BETA*, Winter 2004).

At the February Retrovirus conference, however, Richard Elion, MD, from George Washington University (abstract 53) presented results indicating that a once-daily, four-NRTI regimen consisting of Trizivir plus tenofovir can effectively suppress HIV in treatment-naïve individuals. (Unlike the other three drugs in this regimen, AZT has not been shown to be effective when used once daily.) This interim analysis from study COL40263 included data from 88 subjects who had taken the four-NRTI regimen for at least eight weeks. At 24 weeks 67% achieved viral loads below 50 copies/mL. While this rate is higher than those seen with triple-NRTI regimens, it is lower than those achieved with regimens that include the best available NNRTIs or PIs.

## FDA FAST TRACKS FIXED-DOSE COMBINATIONS

On May 16 DHHS Secretary Tommy Thompson announced a new FDA program that will allow rapid approval of fixed-dose combination (FDC) and copackaged anti-HIV medications for use in developing countries under the Presidential Emergency Plan for AIDS Relief (PEPFAR). The new process will enable companies to submit existing data from past studies and peer-reviewed literature, rather than conducting new trials, and will waive the usual \$500,000 application fee. Applicants will be required to show that the drugs in an FDC retain their bioavailability and do not interact in a detrimental manner. Thompson suggested that the expedited process could take as little as 2–6 weeks.

Some advocates contend that the new FDA process is wasteful duplication of effort, since the World Health Organization (WHO) already prequalifies FDCs for HIV therapy. The new process applies to both brand name and generic manufacturers; however, FDCs containing generic components could not be distributed in the U.S. or other developed countries due to patent laws. The WHO has qualified generic d4T/3TC/nevirapine combination pills produced by the Indian companies Ranbaxy and Cipla, as well as versions of d4T/3TC and AZT/3TC. (However, Cipla's generic 3TC and AZT/3TC were removed from the WHO's approved products list in late May due to poor documentation at an independent laboratory used by Cipla.) The only combination pills currently available in the U.S., Combivir (AZT/3TC) and Trizivir, contain drugs patented by the same company (GlaxoSmithKline).

No one yet makes a fixed-dose pill containing AZT/3TC/efavirenz. But following the administration's recent announcement, Bristol-Myers Squibb, Gilead Sciences, and Merck & Co. announced that they plan to seek approval for an FDC comprised of efavirenz, tenofovir, and emtricitabine (FTC, Emtriva; an NRTI similar to 3TC). Gilead also announced that the FDA granted priority review for its two-drug tenofovir/emtricitabine combination pill, which the company says could be approved by September. In addition, GlaxoSmithKline and Boehringer Ingelheim said they were negotiating a copackaged anti-retroviral combination, most likely nevirapine plus Combivir.

## CARDIOVASCULAR COMPLICATIONS

Much recent HIV research has focused on cardiovascular complications in individuals receiving antiretroviral therapy. According to a report in the January issue of *Stroke*, people with AIDS are more likely than the general population to have strokes (cerebrovascular accidents) at young ages. John Cole, MD, of the University of Maryland at Baltimore and colleagues examined the medical records of 557 individuals aged 15–44 who had strokes between 1988 and 1991; 386 had ischemic strokes (blocked blood

flow in the brain) and 171 had intracerebral hemorrhages (bleeding in the brain). Twelve stroke patients (2.2%), six with each type, were found to have an AIDS diagnosis. After adjusting for age, sex, and race, the relative risk of stroke was 17.8 times greater for people with AIDS. This study, based on events that occurred prior to the advent of HAART, suggests that HIV itself appears to increase the risk of stroke (e.g., by promoting clot formation or causing blood vessel damage), independent of the impact of anti-retroviral therapy.

Another study, reported in the January 2004 issue of *American Heart Journal*, found that HIV positive individuals are more likely than their HIV negative counterparts to experience myocardial infarctions (MIs, heart attacks), and at younger ages. In a study of 690 HIV positive subjects (mostly men), Philip Varriale, MD, and colleagues from Cabrini Medical Center found that 29 individuals (about 4%) were diagnosed as having had an acute MI; 22 of these (about 76%) were younger than 55 years of age and more than half were taking PIs. Among the MI patients, more than 75% of those below age 55 and about 70% of those above this age had either one or no cardiovascular risk factors, leading the authors to suggest that HIV itself, rather than metabolic complications associated with HAART, contributed to coronary artery disease. The authors hypothesized that HIV, by causing endothelial (blood vessel lining) injury, may “initiate the inflammatory process of early atherosclerosis,” eventually resulting in MI as coronary arteries progressively narrow and deprive the heart of oxygen.

Priscilla Hue, MD, and colleagues from UCSF reported in the April 2004 issue of *Circulation* that people with HIV have a higher risk of atherosclerosis (hardening and clogging of the arteries), associated with classic cardiovascular risk factors such as older age, elevated cholesterol levels, tobacco use, and high blood pressure. This study included 148 HIV positive individuals (average age 45) treated with PI-based HAART for a median 3.3 years, and 63 HIV negative control subjects. Using ultrasonography, the researchers determined that HIV positive subjects had increased thickness of the carotid artery intima-media (inner and middle layers), and that the rate of thickening was more rapid compared with control subjects. Arterial plaque buildup was seen in 45% of HIV positive participants vs 24% of uninfected controls. The researchers also found that atherosclerosis was worse in subjects with the lowest nadir CD4 cell counts, suggesting that HIV itself, or greater immune suppression, has a deleterious effect on blood vessels. In another ultrasound study, published in the April 30, 2004 issue of *AIDS*, Paolo Maggi and colleagues with the Italian PREVALEAT Group found that about 52% of HIV positive subjects treated with PIs had evidence of atherosclerotic lesions in their carotid arteries, compared with about 15% of PI-naive subjects taking NNRTIs, and about 14% of those not on antiretroviral therapy or receiving only NRTIs. The authors suggested that “a periodic ultrasonographic

study of the vascular wall should be included in the follow-up of HIV-infected patients.”

## TREATMENT FOR METABOLIC COMPLICATIONS

Physicians are increasingly prescribing adjunct medications to control metabolic manifestations such as hyperlipidemia and diabetes that may increase cardiovascular risk in HIV positive individuals on HAART. At the Retrovirus conference, James Sosman, MD, from the University of Wisconsin (abstract 77) reported results from a placebo-controlled study showing that pravastatin (Pravachol) decreased levels of LDL “bad” cholesterol and improved endothelial function. In terms of body fat changes, Donald Kotler, MD, of the STARS Trial Investigator Group (abstract 80) reported that low maintenance doses of recombinant human growth hormone kept off abdominal fat after initial higher-dose therapy (see “HIV and Hormones,” page 34).

Studies to date have produced inconsistent data concerning the benefits of rosiglitazone (Avandia), a drug used to treat diabetes. Andrew Carr, MD, and colleagues with the ROSEY Study Group compared rosiglitazone with placebo in 180 HIV positive, HAART-treated subjects (98% men) with fat wasting in the limbs (lipoatrophy), but without diabetes. The results were presented at the Retrovirus conference (abstract 79) and published in the February 7, 2004 issue of *The Lancet*. After 48 weeks, no differences in peripheral fat gain or other body composition parameters were seen in the two arms. Limb fat did increase somewhat in the rosiglitazone arm, but also increased to a similar degree in the placebo group. Rosiglitazone was associated with elevated total cholesterol, LDL cholesterol, and triglyceride levels (not usually seen in HIV negative diabetics using the drug), improved fasting insulin levels (even though no subjects in this study were diabetic), and decreased levels of the liver enzyme alanine transaminase (ALT)—likely because the drug improved hepatic steatosis (fatty liver). “Rosiglitazone cannot be recommended for the treatment of HIV lipoatrophy in adults receiving antiretroviral therapy,” the researchers concluded, “even though it has insulin-sensitizing effects in this population.”

But a small study published in the May 18, 2004 issue of the *Annals of Internal Medicine* suggests that rosiglitazone may help improve metabolic abnormalities associated with HAART. Colleen Hadigan, MD, and colleagues from MGH and Harvard Medical School treated 27 HIV positive individuals with lipoatrophy and elevated insulin levels (an indicator of insulin resistance) with rosiglitazone or placebo. After three months, subjects receiving rosiglitazone showed improved insulin sensitivity, decreased fatty acid levels, increased adiponectin (a hormone produced by fat cells), and increased subcutaneous leg fat. However, they also had increased levels of total and LDL cholesterol. Given the inconsistent results of these two studies, more research is needed to determine whether rosiglitazone can

help reduce cardiovascular risk factors in individuals receiving antiretroviral therapy.

Finally, in the February 20, 2004 issue of *AIDS*, Susan Driscoll, NP, and colleagues from MGH reported that a combination of exercise and use of the antidiabetes drug metformin (Glucophage) significantly improved cardiovascular risk factors in individuals taking HAART. In this study, 37 participants with lipodystrophy and insulin resistance were randomly assigned to receive either metformin alone or metformin in conjunction with a program of thrice-weekly aerobic exercise and weight training for 12 weeks. Subjects in the metformin plus exercise arm experienced greater benefit than those receiving metformin alone in the following areas: decreased blood pressure, reduced abdominal fat, improved fasting insulin levels, increased muscle mass, and improved exercise capacity; improvements in lipid profile, however, were similar in the two groups.

## HIV AND COGNITIVE IMPAIRMENT

Although the rate of HIV-associated dementia or HIV-related cognitive-motor complex (formerly called AIDS dementia complex) has decreased markedly since the advent of HAART, cognitive impairment still appears to be more common among HIV positive individuals over age 50 than among HIV negative individuals in the same age bracket. Cognitive impairment in older HIV positive people was addressed in several reports published in a January 2004 *AIDS* supplement devoted to HIV and aging.

Mariana Cherner, PhD, from UCSD and colleagues reported that HIV positive individuals over age 50 were more likely to have neuropsychological impairment than those under age 35 (64% vs 54%), even though the older group had lower viral load levels in the blood and cerebrospinal fluid (CSF) and were more likely to be taking HAART. Victor Valcour, MD, and colleagues with the NeuroAIDS Specialized Neuroscience Research Program reported preliminary data from an ongoing study of cognitive ability in older HIV positive people. Among the first 47 enrolled subjects over age 50, 56% retained normal cognitive function, compared with 88% of the first 32 subjects aged 20–40. The researchers suggested that cognitive impairment in older HIV positive individuals may be attributable to a synergy between HIV-associated dementia and other types of dementia such as Alzheimer’s disease, or may be due to vascular (blood vessel) pathology. In another study, James Becker, PhD, and colleagues from the University of Pittsburgh found that alcohol or drug use or dependence and higher HIV viral load were predictive of cognitive disorders, while a higher level of education appeared to be protective.

Looking at mechanisms underlying cognitive problems in 46 HIV positive, treatment-naïve subjects and 58 HIV negative subjects, Thomas Ernst, PhD, and Linda Chang, MD, from the University of California at Los Angeles found that HIV positive individuals showed notable differences in brain anatomy and chemistry. “In the basal ganglia, HIV

infection appeared to induce neuronal damage or loss beyond that observed in normal aging,” the authors concluded. “In the frontal white matter, HIV infection seemed to exacerbate glial [brain support cell] activation beyond that observed in normal aging.” In related research, Yan Xu from Thomas Jefferson University and colleagues reported in the April 21, 2004 issue of the *Proceedings of the National Academy of Sciences* that certain proteins (e.g., gp120) produced by HIV appear to accelerate the death of central nervous system (brain and spinal cord) neurons, possibly leading to HIV-related encephalopathy. This research team previously showed that HIV was associated with neuronal apoptosis (programmed cell death). In this laboratory study, they introduced HIV-infected T cells and macrophages, or immune cells from which virus had been removed, to neuron cell cultures. HIV-infected T cells induced neuronal apoptosis, but once the virus was removed, these immune cells themselves did not have a deleterious effect. Macrophages induced apoptosis whether or not they contained HIV, but the infected macrophages were significantly more neurotoxic. The authors concluded that HIV and its proteins have a direct neurotoxic effect, in addition to triggering immune cells to produce cytokines that kill neurons.

Finally, in the April 15, 2004 issue of the *Journal of AIDS (JAIDS)*, Kevin Robertson, PhD, from the University of North Carolina at Chapel Hill and colleagues reported that HAART improved neurological functioning in people with HIV even though many antiretroviral drugs have a limited ability to cross the blood-brain barrier. In this prospective longitudinal study, 48 HIV positive subjects received neurological and neuropsychological examinations immediately before and six months after starting HAART. Viral load decreased in both the blood and CSF after the initiation of antiretroviral therapy, and neurological and neuropsychological functioning improved significantly. “[D]espite the poor central nervous system penetration of most of these agents,” the authors concluded, “there is satisfactory short-term improvement in both central nervous system viral burden and nervous system function with HAART.”

## HAART BENEFITS WOMEN WITH ADVANCED DISEASE

The latest results from the WIHS cohort indicate that many women with advanced HIV disease benefit from HAART despite having very high viral loads or very low CD4 cell counts before starting therapy. In the present analysis, which included data from 1,132 HIV positive women followed for a median of about four years, Kathryn Anastos, MD, of Montefiore Medical Center and colleagues examined how well viral load levels and CD4 cell counts before and after starting HAART predict eventual clinical outcome; results were reported in the February 17, 2004 issue of the *Annals of Internal Medicine*. The researchers found that women whose CD4 cell counts remained below

200 cells/mm<sup>3</sup> after starting HAART were more than twice as likely to die from any cause, and nearly 50 times more likely to die of AIDS-defining illnesses, compared with women whose CD4 cell counts rose above 350 cells/mm<sup>3</sup> with treatment. Likewise, women with HIV viral loads above 10,000 copies/mL while on HAART were more than three times as likely to die of any cause than women with viral loads below 80 copies/mL. For women with CD4 cell counts between 200 and 350 cells/mm<sup>3</sup> and/or viral loads between 80 and 10,000 copies/mL after starting HAART, death rates were similar to those seen in the higher CD4 cell bracket and the lower viral load bracket. This study indicates that women’s viral load levels and CD4 cell counts after starting HAART are more accurate predictors of HIV disease progression than pretreatment measurements. “Pre-HAART CD4 cell count and HIV-1 RNA level were not predictive of clinical outcomes if adjusted for values attained after HAART initiation,” the authors concluded. “[E]ven advanced immune suppression can be overcome with HAART” if therapy increases the CD4 cell count above 200 cells/mm<sup>3</sup> and pushes viral load below 10,000 copies/mL.

## NEW GONORRHEA TREATMENT RECOMMENDED FOR GAY MEN

Sexually transmitted diseases (STDs) other than HIV are an increasing concern in the gay community, with rates of infections such as syphilis, chlamydia, and gonorrhea increasing among gay and bisexual men—especially young men—in several U.S. cities. While many STDs can be treated, drug-resistant pathogens are a growing problem. In April the CDC recommended a change in the standard treatment for gonorrhea in men who have sex with men; the new guidelines were published in the April 30, 2004 issue of *Morbidity and Mortality Weekly Report*. According to the agency, fluoroquinolone antibiotics such as ciprofloxacin (Cipro) should no longer be used as first-line treatment for gay and bisexual men due to the rise of drug-resistant *Neisseria gonorrhoeae*. Drug-resistant gonorrhea is common in Asia, and first appeared in the U.S. on the West Coast about four years ago; since 2002 the CDC has recommended that fluoroquinolones should not be used to treat gonorrhea in Hawaii and California. The nationwide prevalence of fluoroquinolone-resistant gonorrhea among men who have sex with men doubled between 2002 and 2003, and now accounts for about 5% of cases. However, resistance rates are considerably higher in some cities (e.g., an estimated 20% in San Francisco and 12.5% in New York City). CDC officials called the rise in drug-resistant gonorrhea in this population “alarming,” since it suggests these men are engaging in unprotected sexual activity; moreover, individuals with gonorrhea can more easily transmit and contract other STDs, including HIV.

Instead of ciprofloxacin, the CDC now recommends cephalosporin antibiotics such as ceftriaxone (Rocephin) or

cefexime (Suprax) for men who have sex with men, regardless of their sexual self-identification. Unfortunately, while ciprofloxacin is given as a single oral dose, ceftriaxone must be administered by injection. Cefexime tablets have been unavailable in the U.S. since the manufacturer's patent expired in 2002, although they might be found for sale online. A new tablet formulation produced by the Indian company Lupin was approved this past February and should be on the market soon (a liquid suspension is currently available). Ciprofloxacin remains the treatment of choice for heterosexuals, except in Hawaii and California, because fluoroquinolone-resistant gonorrhea is still uncommon (less than 1%) in this population.

## RISKS OF METHAMPHETAMINE

Several recent journal articles have examined the deleterious effects of methamphetamine ("crystal") use in people with HIV, including a review of patterns of use and impact on HIV disease progression by Anthony Urbina, MD, and Kristina Jones published in the March 15, 2004 issue of *Clinical Infectious Diseases*. Research has shown that crystal use is associated with unprotected sex, and use of shared needles to inject the drug also contributes to HIV transmission. Laboratory and animal studies have shown that methamphetamine accelerates retrovirus replication, and the drug appears to impair immunological function. Urbina and Jones concluded that "methamphetamine abuse represents a new challenge in HIV treatment and prevention."

In the December 15, 2003 issue of *JAIDS*, Dianne Langford, PhD, and colleagues from UCSD reported that methamphetamine worsens damage to brain cells in individuals with HIV-related encephalitis, a progressive condition characterized by cognitive and motor impairment. The researchers studied the brains of 77 individuals who had died of AIDS. The brains of methamphetamine users showed greater loss of specific subsets of neurons (especially in the frontal cerebral cortex), more neuronal degeneration, a reduced number of synapses, and greater proliferation of support cells called microglia. Surprisingly, however, a review of the subjects' medical records revealed that fewer methamphetamine users than nonusers had been diagnosed with HIV-related encephalitis.

The same week in the *Journal of Infectious Diseases*, Ronald Ellis, MD, and colleagues (also with the UCSD team) reported results from a study of 230 men showing that current methamphetamine users had significantly higher HIV blood viral loads than either previous users or those who had never used the drug (nonusers); past users responded as well as nonusers. Among men on HAART, 39% of current users, 59% of past users, and 62% of nonusers had undetectable blood viral loads. CSF viral loads were also somewhat higher in current users. Notably, the difference was apparent only in methamphetamine users receiving HAART, leading the researchers to suggest that methamphetamine use may reduce the effectiveness

of antiretroviral therapy. The observed difference may be due to poorer adherence in methamphetamine users, although reported adherence was similar in all groups. Methamphetamine may also affect concentrations of antiretroviral medications; interactions between street drugs and anti-HIV therapy have not been well studied. For more information on harm reduction for gay and bisexual men who use methamphetamine, see [www.tweaker.org](http://www.tweaker.org).

## HAART REDUCES HIV INFECTIVITY

According to a study by Travis Porco, PhD, and colleagues from UCSF published in the January 2, 2004 issue of *AIDS*, use of HAART may reduce HIV infectivity by 60% or more. Effective anti-HIV therapy decreases viral load, and research has shown that people with low or undetectable viral loads are less likely to transmit the virus to their sexual partners; mutant drug-resistant HIV strains selected by treatment may also be less transmissible than wild-type virus. Using data from 534 initially seronegative gay or bisexual men aged 18–29 enrolled in the San Francisco Young Men's Health Study, the researchers created a mathematical model showing that the per-partner probability of HIV transmission decreased from 0.120 before the advent of HAART to 0.048 after HAART came into widespread use—a decline of 60%. Over the same period, however, rates of self-reported unprotected sexual activity increased, from an average of 0.6 unprotected receptive anal sex partners during 1994–1995 to 1.3 during 1997–1999. Thus, while antiretroviral therapy may play a role in preventing HIV transmission, this effect may be offset by increases in unprotected sex, resulting in an overall stable or rising rate of new infections. "Use of HAART is a potentially important HIV prevention tool," the researchers concluded, but "one that is likely to succeed...only if accompanied by continued emphasis on avoidance of exposure."

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## CORRECTION NOTICE

The following errors appeared in the print edition of Winter 2004 *BETA*. Boehringer Ingelheim should be noted as the developer of tipranavir. On page 20, the second question of the brief, two-question depression screen should read: "Are you *unable* to enjoy...." And several occurrences of *incidence* and *prevalence* are reversed. The corrected version of the Winter 2004 edition is available online (see [www.sfaf.org/beta](http://www.sfaf.org/beta) or [www.thebody.com/sfaf/sfafix.html](http://www.thebody.com/sfaf/sfafix.html)).

## THE PIPELINE:

### Three to Watch

John Hawes

Four antiretroviral drugs were approved in 2003: emtricitabine (FTC, Emtriva), a nucleoside reverse transcriptase inhibitor (NRTI); the protease inhibitors (PIs) atazanavir (Reyataz) and fosamprenavir (Lexiva); and T-20 (enfuvirtide, Fuzeon), the first of a new anti-HIV drug class, entry inhibitors.

While this is certainly good news, the likelihood that an antiretroviral drug will be approved in 2004 seems slim. Currently only one compound—Boehringer Ingelheim's PI, tipranavir—is in Phase III clinical trials (see "Tipranavir: the First Nonpeptidic Protease Inhibitor," *BETA*, Winter 2004, and "Open Clinical Trials" on page 50 of this issue). Yet no oral or poster presentations on tipranavir were presented at the 11<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, the major annual venue for new basic and clinical research related to HIV infection, held February 8–11 in San Francisco.

In fact, this year's meeting did not have an entire oral session devoted solely to investigational compounds as in the past. There was one session on the pharmacology (composition and effects) of new agents, but most of the presentations were of research on already approved drugs. And while there were numerous posters on new compounds, most concerned either laboratory or early clinical studies.

While the relatively empty drug pipeline is discouraging, there were three isolated oral presentations at the Retrovirus conference that offered new data on the use of investigational anti-HIV agents in people with HIV. These presentations reported results from early Phase I/II clinical trials of D-D4FC, a new NRTI; SCH-D, a coreceptor antagonist; and the attachment inhibitor BMS-488043. This issue's Drug Watch will discuss these aspiring drug candidates and why they are three to watch.

### D-D4FC, a Potent New NRTI

D-D4FC (Reverset, formerly known as DPC-817) is a new drug from an old class of antiretrovirals—the NRTIs, which include drugs such as AZT (zidovudine, Retrovir) and 3TC (lamivudine, Epivir). Since drug resistance is an increasing problem, much of the current research into new drugs from the existing classes of antiretrovirals is directed at compounds that are effective against resistant virus. D-D4FC is no exception. *In vitro* (laboratory) studies have shown that D-D4FC has potent antiviral activity against HIV strains resistant to other NRTIs, including AZT, 3TC, and tenofovir DF (Viread). Of note, evidence of mitochondrial toxicity, which is associated with this class, has not been seen in studies of D-D4FC to date.

The results of the first Phase II study of D-D4FC, and the first data on the use of this investigational agent in people with HIV, were presented at the Retrovirus conference by Robert Murphy, MD, from Northwestern University in Chicago. These preliminary results showed that D-D4FC—when given without any other anti-HIV medications to people who had never been treated—caused dramatic reductions in viral load after only ten days of treatment.

Thirty HIV positive, treatment-naïve individuals (24 men, six women) with CD4 cell counts above 50 cells/mm<sup>3</sup> and viral loads above 5,000 copies/mL were enrolled in this monotherapy dose-escalation study. Subjects were randomized to one of three once-daily doses of D-D4FC—50, 100, or 200 mg—or placebo for ten days. The study was double-blinded, which means that neither the subjects nor the clinicians knew who was taking what dose of the study drug or who was taking the placebo. At the start of the trial, the mean (average) baseline viral load was 4.49 log copies/mL (roughly 30,000 copies/mL) and the mean CD4 cell count was 468 cells/mm<sup>3</sup>.

At the end of the ten-day treatment period, the mean viral load in the people receiving D-D4FC dropped by approximately 1.7 log copies/mL, about a 95% decrease from baseline levels. For the different dose groups, the mean reductions from baseline were 1.67, 1.74, and 1.77 log copies/mL for the 50, 100, and 200 mg doses, respectively. Safety evaluations revealed that all adverse events, including headache and fatigue, were mild or moderate and occurred at similar rates in the active drug and placebo groups.

D-D4FC's effect on viral load compared favorably with that of other potent NRTIs, such as emtricitabine, 3TC, and tenofovir. Importantly, no serious drug-related adverse events were reported; however, it should be kept in mind that this study's duration was less than two weeks. D-D4FC has a long half-life (13–17 hours) and is orally bioavailable, which means that it could potentially be used as a once-daily oral treatment.

Based on the results of this early clinical trial and the drug's effectiveness against drug-resistant HIV, D-D4FC is being evaluated further in longer studies in people who have previously been treated with other antiretrovirals. The drug was discovered by Pharmasset and is being developed by Incyte. (For more information, see "Open Clinical Trials" on page 50.)

## SCH-D, Another Attempt at Coreceptor Blocking

SCH-D (also known as SCH 417690) belongs to the same broad class of entry inhibitor drugs as T-20. However, while T-20 is a fusion inhibitor that blocks HIV from fusing with a host (human) cell after attaching to its membrane, SCH-D is a coreceptor antagonist that attempts to prevent HIV from initially binding to a host cell by blocking an essential coreceptor. In order to attach to a cell and gain entry, HIV requires two things: a CD4 receptor that resides on the surface of certain human cells, and a secondary receptor, or coreceptor. Depending on the type of HIV strain, the virus uses either the CCR5 or the CXCR4 coreceptor to complete its attachment to the cell's surface.

In laboratory studies, SCH-D has been found to bind specifically to CCR5 coreceptors (which appear to be most commonly used by HIV) and to effectively block a wide range of HIV isolates from attaching to cells. Compared with SCH-C, an earlier Schering-Plough coreceptor candidate no longer in development, SCH-D is about ten-fold more potent and appears not to cause heart toxicity, the downfall of its sister compound. Unlike T-20, SCH-D can be taken orally. Results of the first use of this CCR5 coreceptor antagonist in people with HIV were reported at this year's Retrovirus conference.

Mark Laughlin from Schering-Plough presented results of a 14-day study that was similar in design to the D-D4FC study. For 14 days, 48 people chronically (i.e., not recently) infected with HIV received only SCH-D at twice-daily doses of 10, 25, or 50 mg, or were given a placebo. Those participating in the study had not taken antiretroviral drugs in the previous eight weeks and had CD4 cell counts greater than 200 cells/mm<sup>3</sup>. The mean baseline viral load for the treatment groups ranged from approximately 36,000 copies/mL for the 10 mg dose group to over 100,000 copies/mL for the 50 mg dose group. The mean CD4 cell count ranged from 369 to 486 cells/mm<sup>3</sup>.

SCH-D demonstrated increasing antiviral activity over this range of doses, with the highest dose resulting in a 1.62 log reduction in viral load by the end of the two-week treatment period. Notably, 81% of the subjects in the highest dose group achieved a greater than 1 log drop (greater than 90% decrease from baseline) in their viral load. Mean viral load reductions with the other doses were also greater than 1 log: 1.08 and 1.56 log copies/mL for the 10 and 25 mg doses, respectively. The drug appeared to be safe and well tolerated in all dose groups.

This study is further proof that compounds that inhibit binding of the virus to secondary attachment receptors can reduce viral replication when used in people infected with HIV. (A Phase II study of SCH-D is now enrolling; see "Open Clinical Trials" on page 50.)

## BMS-488043, a Novel Attachment Inhibitor

Another investigational agent that represents a new anti-HIV drug class is BMS-488043, a compound being developed by Bristol-Myers Squibb. Like Schering's compound, BMS-488043 is also an attachment inhibitor, but this agent blocks attachment by binding to the virus rather than a human cell. HIV uses a molecule on its surface called gp120 to attach to a cell's CD4 receptors. BMS-488043 blocks viral entry by selectively binding to gp120 and preventing HIV from attaching to a CD4 receptor. One benefit of attacking HIV in this manner is that attachment is blocked regardless of the type of cell coreceptor present. (In contrast, SCH-D will work only for cells that have CCR5, rather than CXCR4, coreceptors.) Results from studies in healthy, HIV negative volunteers indicated that BMS-488043 could be given orally and had a good safety profile. The results of an early Phase I clinical study in HIV positive individuals were presented at the Retrovirus conference by George Hanna of Bristol-Myers Squibb.

The antiviral activity of BMS-488043 was evaluated in a placebo-controlled, multiple-dose study in 30 HIV positive adults (26 men, four women). Participants were antiretroviral-naïve or had not taken any antiretroviral medication for at least 16 weeks before study entry; 14 of the 30 had previously taken antiretroviral therapy. Subjects had CD4 cell counts above 250 cells/mm<sup>3</sup> and viral loads between 5,000 and 500,000 copies/mL; at study entry the mean viral load was 4.61 log copies/mL (approximately 40,000 copies/mL) and the mean CD4 cell count was 399 cells/mm<sup>3</sup>. Participants received either 800 or 1,800 mg oral doses of BMS-488043 or placebo twice daily for seven days.

After seven days, BMS-488043 monotherapy produced an approximately ten-fold reduction in mean viral load, with the majority of participants in both dose groups experiencing a 1 log or greater decrease. However, the mean reduction in viral load eight days after the start of treatment (that is, one day after treatment ended) was just under 1 log: 0.72 and 0.96 log copies/mL in the 800 and 1,800 mg dose groups, respectively. Nevertheless, these reductions still represented nearly a 90% drop in the subjects' viral loads, including those who had received prior antiretroviral therapy. Mild to moderate side effects included fatigue, headache, insomnia, and diarrhea. No serious adverse events were noted.

This study is the first demonstration (in other words, a "proof of concept") that a drug that binds to the virus rather than a host cell can reduce viral replication in

humans and supports further evaluation of compounds belonging to this new antiretroviral class. Phase II research of BMS-488043 is expected to begin in late 2004.

## Conclusion

An important reason to focus on these three new compounds, besides the potency and relative safety suggested by these early studies, is that each of them represents a different method of attacking HIV. The problem of drug resistance, and the role it plays in treatment failure, is growing—not only among those who currently are on treatment, but also in people who have never been exposed to antiretroviral therapy. The latter situation can occur when a person is infected with a drug-resistant HIV strain. HIV is increasingly becoming resistant to the currently available drugs in the first three antiretroviral classes, as well as to T-20, the only currently approved member of the fourth (entry inhibitor) class. New drugs that can durably suppress viral load in people with resistant virus are urgently needed. By attacking the virus using drugs with different mechanisms of action, the problem of viral resistance may be overcome enough to ensure that people with HIV will always have adequate treatment options. The three investigational drugs described here represent promising first steps in that direction.

## *glossary*

**half-life:**

the time required for half the total amount of a drug to be eliminated from the body.

**mitochondrial toxicity:**

damage to the mitochondria as a side effect of drugs, which can lead to lactic acidosis, a potentially fatal buildup of lactic acid in the blood.

**placebo:**

an inactive substance (e.g., a “sugar pill”) or mock therapy.

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# BACKLASH

## over Ritonavir Price Hike

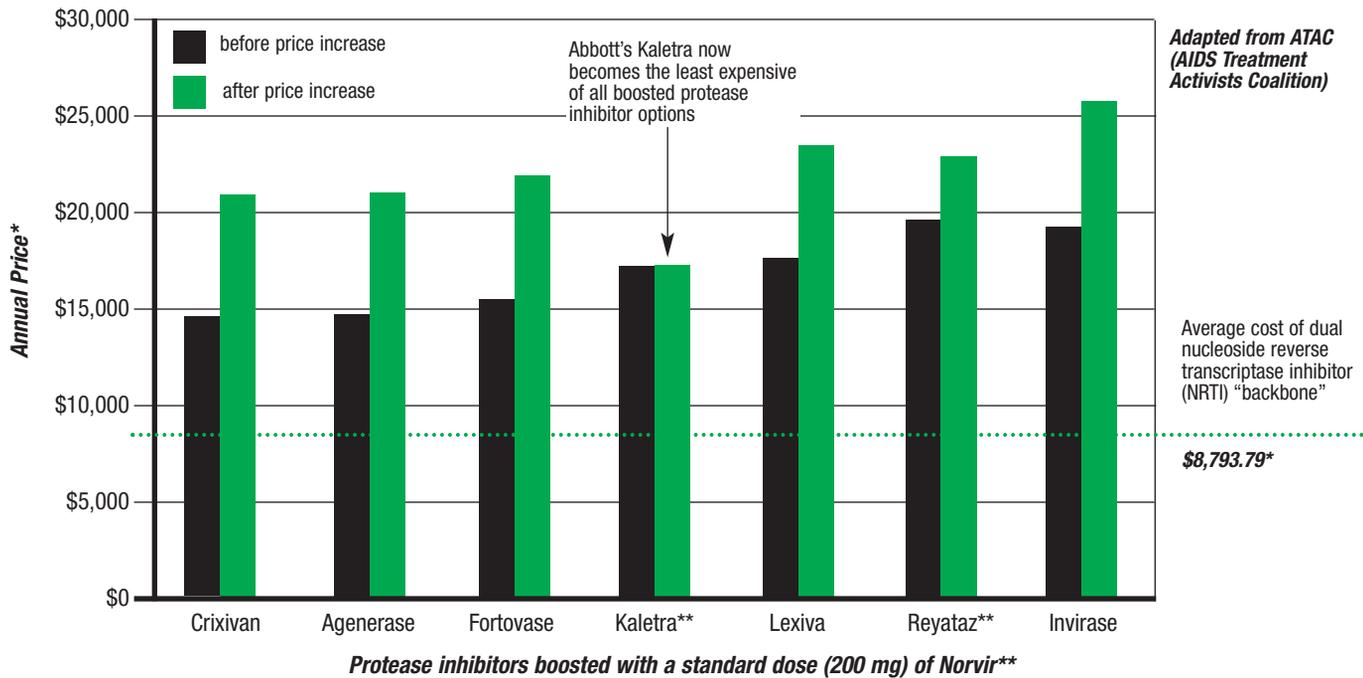
**Bob Huff**

On December 3, 2003, Abbott Laboratories, the pharmaceutical company that makes lopinavir (Kaletra), announced that it was going to raise the price of its other anti-HIV drug, ritonavir (Norvir), from \$2.14 to \$10.72 per capsule in the U.S.—an increase of 400%. (These prices reflect the Average Wholesale Price, or AWP, a national average of list prices charged by wholesalers to pharmacies.)

Originally approved and marketed as a protease inhibitor (PI) at a dose of 12 capsules per day, ritonavir is now primarily used at a much lower dose to help boost the blood levels of other PIs. At the new price, the cost of some ritonavir-boosted antiretroviral combinations has as much as doubled, while the price of Abbott’s PI Kaletra, which contains a small boosting dose of ritonavir in its formulation, remains unchanged. Abbott claimed that the price increase was a necessary adjustment that “reflects the value that ritonavir brings to combination therapy.” For many activists, clinicians, and government officials, however, the price hike was interpreted as a business move calculated to force a switch from other boosted PIs to Kaletra.

Within a week of the announcement, members of the AIDS Treatment Activists Coalition (ATAC) confronted Abbott representatives attending the North American Treatment Action Forum (NATAF) conference in Phoenix. ATAC members distributed flyers that depicted Abbott as a vulture “feeding on the bones of the health-care system,” and argued that the ritonavir price hike threatened treatment options for people with HIV, especially people with multidrug-resistant virus that are particularly dependent on ritonavir-boosted salvage regimens. They also worried that drug companies developing new salvage drugs might reconsider their financial commitment if a dependency on ritonavir threatened to price them out of the market.

**EFFECT OF RITONAVIR (NORVIR) PRICE HIKE ON THE ANNUAL COST OF BOOSTED PROTEASE INHIBITOR-BASED REGIMENS**



*\*All values based on Average Wholesale Prices (AWP) as published by First DataBank, based on national surveys of prices charged by pharmaceutical wholesalers. The AWP is the benchmark price used by public and private purchasers. [www.firstdatabank.com/customer\\_support/faqs](http://www.firstdatabank.com/customer_support/faqs).*

*\*\*Kaletra already contains ritonavir in its formulation. Atazanavir (Reyataz) is boosted with only 100 mg of ritonavir.*

Furthermore, the activists feared that such a shocking price jump could give the green light for other pharmaceutical companies to raise prices, putting a fatal strain on the budgets of cash-strapped state AIDS Drug Assistance Programs (ADAPs) that cover anti-HIV drug costs for underinsured people who cannot afford their medications (see “ADAP in Peril” on page 27).

As word of Abbott’s stunning move spread, reaction started to come from unlikely sources. Graeme Moyle, MD, of Chelsea and Westminster Hospital in London, an area not even affected by the price change, called for a boycott of Abbott products. In the U.S., the two professional organizations for HIV specialists, the American Academy of HIV Medicine (AAHIVM) and the HIV Medicine Association (HIVMA), each issued strong letters of criticism calling on Abbott to rescind the price increase, citing the expected burden for ADAPs that were already instituting waiting lists and tightening eligibility restrictions.

In response, Abbott pledged to permanently freeze the price of ritonavir for ADAPs and other government programs at the old price. The company has also set up a liberal patient assistance program (PAP), which it said will guarantee that any uninsured person who needs ritonavir will be able to obtain the drug for free. Abbott has also offered to supply ritonavir at the old price to research programs approved before the price hike, and has said it will

attempt to arrange special terms for developers of new salvage drugs that will depend on ritonavir boosting. All of this, the company said, would ensure that the price increase is invisible to individuals who need the drug. Yet as the new price went into effect during the first week of 2004, anger at Abbott continued to grow.

In late January over 175 prominent HIV physicians signed a letter calling for a boycott not only of Abbott products, but also of its sales representatives, marketing events, and research programs. The letter termed Abbott’s act “outrageous behavior, extremely disappointing from a company that was at the vanguard during the early stages of the HAART era.”

In early February the 11<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, the most important annual scientific meeting on HIV, was held in San Francisco. Although not usually an occasion for social or political expression, this year’s conference was remarkable for the manifestations of anger and protest over the ritonavir issue. Even more remarkable was that the most visible protest leaders were HIV clinicians, who, as a group, rarely engage in AIDS activism. During an afternoon break on the second day of the conference, about 30 physicians representing the newly formed Organization of HIV Healthcare Providers gathered in front of the Moscone West Center and marched two blocks to a press conference held at the

San Francisco AIDS Foundation offices. There, William Powderly, MD, of St. Louis; Benjamin Young, MD, of Denver; and Edwin DeJesus, MD, of Miami explained the necessity of resisting the ritonavir price hike. Addressing the cameras of CNN and San Francisco news outlets in the packed meeting room, the physicians pledged to boycott Abbott's sales representatives, resign from Abbott advisory boards, and refuse to participate in nonessential Abbott research.

The Abbott backlash was gaining momentum. In late January the Consumer Project on Technology, a Washington, DC, consumer organization, formally requested that Tommy Thompson, the director of the Department of Health and Human Services (DHHS), invoke a little-known law that would allow the government to terminate Abbott's patent monopoly on ritonavir and allow generic drug makers to produce the medication for sale within the U.S. at affordable prices. The law, a hitherto unexercised 1986 provision of the 1980 Bayh-Dole Act that liberalized access to generic medications in the U.S., gives the government the right to "march-in" on the patent of a drug that has been developed in part with taxpayer money when the patent holder refuses to make the drug available on reasonable terms. Early research on ritonavir was funded by a government grant. The patent itself notes, "This invention was made with Government support under contract number A127220 awarded by the National Institute of Allergy and Infectious Diseases. The Government has certain rights in this invention." And a not-for-profit organization called Essential Inventions has asked DHHS for a license to produce generic ritonavir. The DHHS heard testimony from HIV community advocates, legislators, and Abbott representatives at a May 25 hearing on those rights and the merits of the march-in demand. National Institutes of Health (NIH) director Elias Zerhouni, MD, will make the final decision on the request to circumvent Abbott's patent.

Lawsuits and complaints against Abbott have snowballed since the Retrovirus conference. A San Francisco law firm filed a class-action lawsuit in the U.S. District Court for Northern California on behalf of two anonymous ritonavir consumers who say they have been financially injured by the new price. In Southern California, the AIDS Healthcare Foundation (AHF) filed two lawsuits, one accusing Abbott of unfairly using its monopoly on ritonavir and another claiming false advertising. A Boston-based public interest organization, the Prescription Access Litigation Project (PAL), filed a class-action lawsuit in Illinois charging Abbott with illegal and unjustifiable practices. The attorneys general of Illinois and New York have said they are looking into possible restraint of trade violations by Abbott. Complaints have also been lodged with the Federal Trade Commission (FTC) charging anticompetitive behavior, and with the Food and Drug Administration

(FDA) concerning misleading cost-comparison materials that Abbott produced to defend its action; on June 10 the FDA sent Abbott a warning that these materials were indeed "false and misleading." A front-page article in the *New York Times* on April 15 brought the protest over riton-

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**In late January over 175 prominent HIV physicians signed a letter calling for a boycott not only of Abbott products, but also of its sales representatives, marketing events, and research programs.**

avir to a wider audience. On April 21 a group of physicians and clinical researchers from the HIV Outpatient Study (HOPS), an important national research collaborative group, announced, "It is unconscionable that the dramatic and unjustified increase in ritonavir pricing go unchallenged by the HIV care-giving community." On May 19 a bipartisan group of U.S. senators, including Senate Commerce Committee Chair John McCain (R-AZ) and ranking Democratic committee member Ernest Hollings (D-SC), called on the FTC to investigate Abbott's actions.

Amidst this flurry of protest, dozens of activists from the HIV/AIDS and senior citizen communities of Chicago showed up at the gates of Abbott headquarters in Abbott Park, Illinois, on April 23 to ask that Abbott stock owners attending the annual shareholders meeting demand the company roll back the price of ritonavir. Inside the meeting Abbott officials defended the company's pricing policy and successfully defeated shareholder proposals to require more social accountability from the corporation.

Six months after Abbott blithely announced a 400% increase in the price of ritonavir, the issue shows no signs of going away. While few observers believe a ritonavir price rollback is likely, most agree that Abbott has become a lightning rod for frustration over ADAP waiting lists, Medicaid drug restrictions, and soaring insurance rates, all of which have been traced to the ever-increasing cost of pharmaceuticals. Meanwhile, an across-the-board 4.9% jump in the prices of all GlaxoSmithKline drugs announced in January has gone all but unnoticed by the wider HIV community. As prices rise and cutbacks continue, there will be ample opportunity for the new alliances and activism triggered by the ritonavir outrage to take on any number of emerging threats to quality HIV care that loom on the horizon.

**Bob Huff is editor of *GMHC Treatment Issues*, published by Gay Men's Health Crisis in New York City.**

# Adherence

*adherence: following a prescribed treatment regimen, including correct drug dosages, medication schedules, and food restrictions.*

What are the barriers to treatment adherence, and how can people overcome them?

## Jen Hosler

*Social Worker, Action Point\* — San Francisco*

Every client is different. It's best to assess each person's barriers to adherence, rather than making assumptions. For example, homelessness may be an issue for some clients and not others; some homeless people are very adherent. Some active drug users or clients who seem out of it have excellent adherence, while others who might seem together and are working part-time can't manage a drug regimen.

Depression is common. Sometimes clients are overwhelmed and not sure if they want to continue living, and the meds remind them of their illness or the mistakes they've made in their lives. At Action Point we refer depressed clients to mental health treatment. If a client needs psych meds, we can help manage those along with anti-HIV drugs.

To help improve adherence we try to tailor dosing schedules around the person's daily routine. We give some clients alarm watches to remind them when to take their next dose. We offer one-on-one support; it makes a difference when clients feel that someone cares about their health and the importance of sticking to their drug regimens. The same is true of clients' partners, some of whom are very involved in our clients' health. Basically, anyone in any situation can potentially stay adherent with guidance and support.

## Alix Strough, RN

*Nurse, Action Point — San Francisco*

Everyone has their own story about why it's difficult to take medicines. Some people cite substance use and are afraid to mix antiretrovirals with alcohol and other drugs, or they get caught up with taking street drugs and don't take their anti-HIV meds. Other people have a hard time wrapping their heads around the idea that they have to take medicines very regularly for the long term. Some people lack a stable place to keep their meds and food for taking their meds.

Directly observed therapy [DOT, or watching a person take every dose of medicine] is very useful for some people here at Action Point. Others come in every week or two for Medisets. Others come in two or three times a week because they need extra encouragement; it's helpful for them to talk about their concerns and about what's going on in their lives. Having a good

rapport with the provider can really help reduce adherence barriers for clients.

## Joanne S.

*Larkspur, CA*

The biggest barrier for me is lack of a fixed schedule. Some days I might eat dinner at 7:00 pm, others at 9:00 pm, I go to bed at different times, wake up at different times, so there are no set markers during the day to remind me to take my meds. And the second biggest barrier is the pill burden. I don't have trouble swallowing them, it's the number of pills to take at once that is unpleasant. I've tried different things to create regularity. I was trying to take my pills every night before bed, but I had a lot of problems with that. Then I switched to mornings and it's been better. I tell myself, "Before I start my day, I take my pills."

In general, my adherence hasn't been good; I've had problems since the beginning. My doctor knows I have trouble with adherence, but he doesn't really know how much since my blood work doesn't reflect my troubles. My CD4 counts are always really good, around 700, and my viral load is about 20,000. It's not that he's punitive, but there's so little time to spend with him and so many other things I need to discuss. By the time he's done giving me the adherence lecture, there's no time for anything else.

In fact, I became more regular when I started taking only half doses of medication. But things have changed recently. My husband shared with me that he becomes upset and frightened when I treat my medications casually. So I really examined my motivations and saw that no matter how comfortable I was with my habits, I was still taking a chance with my life. Right now I'm back to the full doses and oddly enough, I'm having no problem staying on schedule. I guess it's the difference between seeing it as an inconvenient chore and seeing it as a lifeline.

## Perry N. Halkitis, PhD

*Assistant Professor and Chair of Applied Psychology*

*New York University — New York City*

I work primarily with gay and bisexual men. For a simplistic answer, the biggest barrier to adherence is life. We don't conceptualize how people will integrate at least 95% adherence into their lives. For some reason, it's expected that HIV positive people will stay adherent all the time, for years, unlike people with other

diseases. It's unrealistic to expect that type of outcome. In the gay community, one of the main barriers is mental health issues, such as depression, loneliness, and stigmatization. Another is illicit drug use, which is consistently shown to be a factor in adherence because it disinhibits people to do what they want. This is especially true of weekend drug users, who take illicit drugs to escape from everything, including their health and taking meds. Chronic illicit drug users find it easier to integrate and "routinize" their drug use behavior into the patterns needed to stay adherent to a HAART regimen. And again, a major barrier is the demands of day-to-day life—work, school, relationships—that impede people from taking meds properly.

## George Endry

Berkeley, CA

Having a busy and active life is a barrier. I've been on a combo for six months, and only in the past month have I figured out a schedule. I'm fairly adherent. I missed a couple of doses in the first few months when I was taking abacavir [Ziagen], my only twice-daily drug. I forgot to take it a few times, so my doctor told me to take it only once a day, and I'm still getting good results—not that anyone should do the same. Most of my meds have to be taken with a full meal or I have light-headedness and nausea. Since I don't always get to eat a full meal at lunch, over time I've been taking all my meds right after dinner so the side effects won't interfere with the day's activities. A real challenge was that the first regimen I was taking failed, but one of those first drugs, 3TC [lamivudine, Epivir], is also in my second combo. Coordinating with the pharmacy for the three drugs in the second regimen was a major hassle. My refill schedule wasn't synchronized, the pharmacy wasn't making it easy for me, and it became a significant barrier to manage whether I had the right amount of drugs, especially if I was going to take a trip. But now I have it worked out so that at the end of the month all three drugs are refilled at the same time. A Mediset definitely helps to remind myself if I've taken a dose. Before HIV I never took much medicine, except antibiotics, so it's been a real shift in my mental model to take drugs so regularly, but I've pretty much worked it out. I try to keep it simple—a simplified regimen, a regular routine, always remembering to keep drugs with me if I'm going out.

## Jack A. DeHovitz, MD, MPH

Director, HIV Center for Women and Children  
SUNY Downstate Medical Center — Brooklyn

The people I work with are primarily indigent, 90% Caribbean or African American, 60% women. Their adherence barriers are children (i.e., their needs and schedules), coexisting drug and alcohol use, perceived or real medication toxicities or side effects, and the need to take more than one dose of medication each day.

As for overcoming barriers, there's no question that once-a-day drugs with no food or water restrictions is the way to go.

## Jim Park

San Francisco

I've been positive for almost 18 years and have gone through all the drugs that have come forward in development, typically

one at a time. The challenge with pills is side effects, especially with certain drugs, like AZT [zidovudine, Retrovir], which makes me nauseous. Timing has been a real challenge. In order to take more than 30 pills per day—which is what I'm doing now—I've had to learn how to space them out without upsetting my stomach. At 9:00 I take the orange pills, at 10:00 I take the blue pills. Timing is also a challenge because I travel a lot for work. My current barrier is fitting T-20 [enfuvirtide, Fuzeon] into my schedule. This drug needs refrigeration, it needs to be mixed, and it has to be injected in a certain way in certain areas. I now have a desktop refrigerator at work to keep a week's supply at the office. If I'm traveling, I need a room with a minibar. If it's a social weekend, I need to bring blue ice packs with me. I have adapted. I'm very precise about maintaining the drugs and the regimen, and it's been really challenging. But I've managed to find ways around the problems with each drug. I'm in the 90% percentile in adherence and it's paid off. I think T-20 literally saved my life.

\* For information about the Action Point treatment adherence program, call 415-487-3030.

## ADHERENCE TIPS

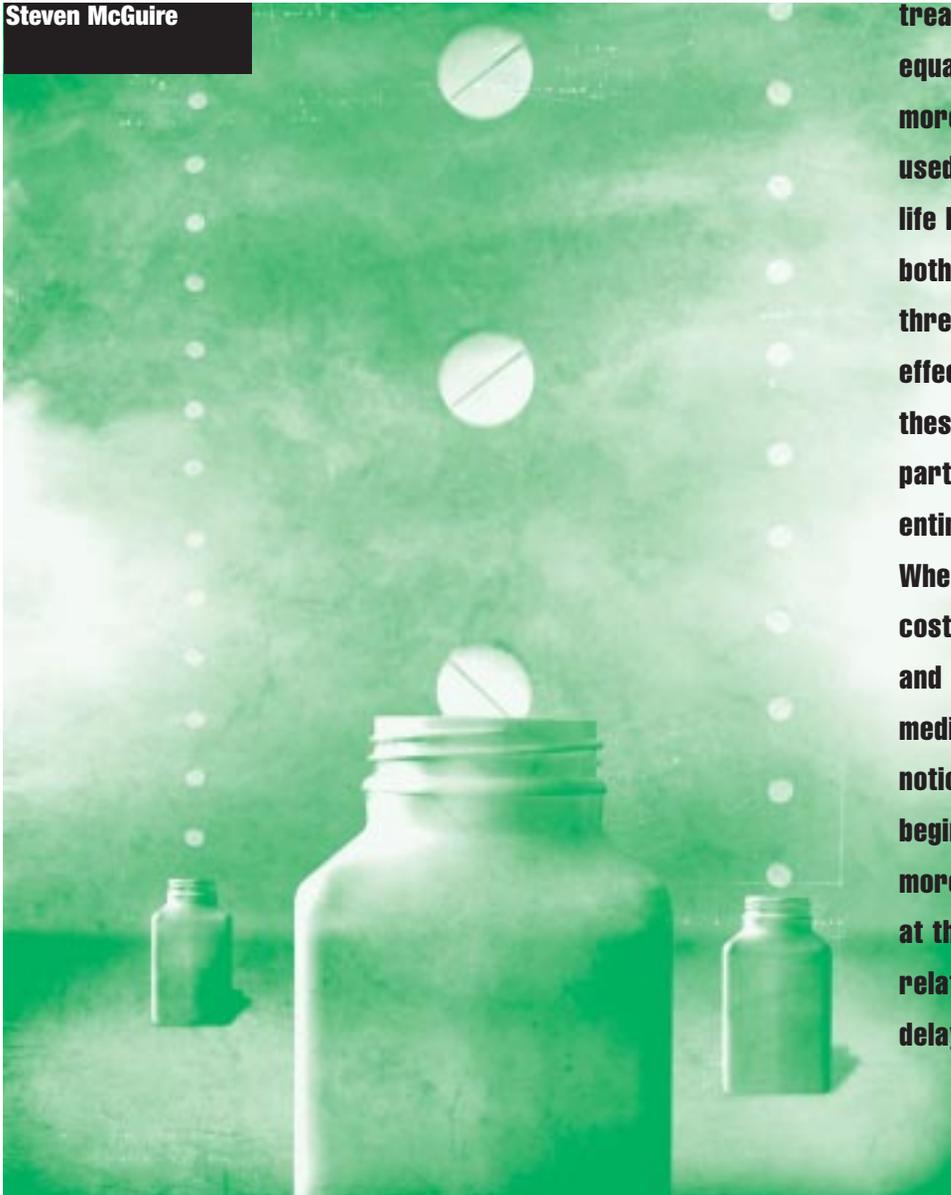
Link taking medication with a routine activity, such as getting dressed in the morning or walking the dog.



Medisets can help. They save time in opening multiple medicine containers and give instant, reliable feedback about whether or not a scheduled dose has been taken.

Talk to a clinician about making the regimen easier. Many drugs have been reformulated, or combined with other drugs, to allow for once-a-day dosing, no fasting or meal requirements, and lower pill counts.

Steven McGuire



In a field of unknowns, few topics are as unsettled as the subject of when to start anti-HIV treatment. The risk vs benefit equation of therapy has become more complicated as the drugs used to fight HIV and prolong life have been associated with bothersome and sometimes life-threatening adverse side effects (even though some of these effects may be only partly drug-related, or may be entirely due to other factors). When issues such as high drug costs, adherence challenges, and aversion to antiretroviral medication are considered, the notion of an optimal time to begin treatment becomes even more elusive. This article looks at the various issues and data related to starting versus delaying anti-HIV treatment.

## Making the Decision to Start Therapy

# On the Level

## Hit Hard, Hit Early?

With the approval of the first protease inhibitor (PI) in 1995, the field of HIV treatment advanced dramatically. Researchers and clinicians found that people who took a triple combination of antiretrovirals, usually one PI and two nucleoside reverse transcriptase inhibitors (NRTIs), could experience significant improvements in their health. Many people taking the new highly active antiretroviral therapy, or HAART, achieved suppression of their HIV viral loads to below the limit of detection of available tests and experienced significant increases in their CD4 cell counts. Fewer opportunistic illnesses (OIs) were seen in people taking HAART, and there were sharp declines in the number of deaths from HIV-related illnesses. Thus began the era of “hit hard, hit early,” with many specialists recommending HAART for most people with CD4 cell

counts below 500 cells/mm<sup>3</sup>, including people without any disease symptoms.

Soon after HAART came into widespread use in the developed world, however, people with HIV and their providers discovered that an array of adverse events seemed to be associated with these effective drugs. Problems included body fat irregularities (wasting and/or fat gain), hyperlipidemia (high levels of blood fats), cardiovascular disease (see “Cardiovascular Disease in People with HIV,” *BETA*, Summer/Autumn 2002), and insulin resistance and diabetes (impaired sugar metabolism; see “Insulin Resistance and Diabetes,” *BETA*, Winter 2004).

Because such adverse events occurred in significant numbers of people taking HAART—which does not cure HIV disease—some clinicians and advocates began to question whether these individuals’ health might be better served by delaying the start of anti-HIV therapy until they

were at greater risk of specific HIV-related illnesses, or even AIDS itself. (AIDS is advanced-stage HIV disease. It is defined as having fewer than 200 CD4 cells/mm<sup>3</sup> or being diagnosed with at least one of over 20 clinical conditions, such as systemic non-Hodgkin’s lymphoma.) As a result of this questioning concerning the best time to initiate HAART, the most recent official HIV treatment guidelines from the U.S. National Institutes of Health (NIH) recommend delaying the start of antiretroviral therapy until an individual’s CD4 cell count declines to 350 cells/mm<sup>3</sup> or below, or viral load rises above 55,000 copies/mL (see sidebar on this page).

## Getting SMART

The NIH’s shift away from the “hit hard, hit early” approach does not mean that the question of when is the best time to start anti-HIV treatment has been definitively answered.

The most recent NIH treatment guidelines (current as of March 23, 2004) make the following recommendations:

CURRENT GUIDELINES

- People who are experiencing symptoms specifically associated with HIV disease (such as enlarged lymph nodes, unexplained weight loss, diarrhea that lasts several weeks, persistent fever or night sweats, or a white coating on the tongue) or who have fewer than 200 CD4 cells/mm<sup>3</sup> should receive treatment.
- People with no symptoms who have either fewer than 350 CD4 cells/mm<sup>3</sup> or viral load over 55,000 copies/mL should be offered treatment. This decision should consider the risk of disease progression and the individual’s willingness and ability to adhere to therapy. Some HIV specialists would delay treatment for people with 200 to 350 CD4 cells/mm<sup>3</sup> and viral loads under 55,000 copies/mL.
- People with no symptoms, more than 350 CD4 cells/mm<sup>3</sup>, and a viral load below 55,000 copies do not need to start treatment. They should continue to get regular viral load and CD4 tests. Some experts, however, would offer HIV therapy to these patients.
- The guidelines published by the International AIDS Society—USA ([www.iasusa.org/pub/press\\_release.html](http://www.iasusa.org/pub/press_release.html)) appear to leave an even wider range of decision-making to individual physicians and their patients: “Physicians and patients must weigh the risks and benefits of starting therapy and make individual informed decisions. . . . It is known that therapy should not be delayed until the CD4<sup>+</sup> count declines to 200 cells/microliter [mL], because of the increased risk of death if therapy is started this late. The point above this level at which it is most beneficial to start therapy is not known. At the higher CD4 cell counts, several other factors are considered, including specific CD4 cell count or decline rate, the viral load level, the patient’s commitment to adhere to therapy, and the risk of side effects.”

[www.aidsinfo.nih.gov/guidelines](http://www.aidsinfo.nih.gov/guidelines)

In fact, many HIV experts feel that the situation is more confusing now than ever. To try to clarify this situation, the federally funded Community Programs for Clinical Research on AIDS (CPCRA) has begun a long-term (up to nine, with an average of seven, years) study of about 6,000 people living with HIV. Called SMART (Strategies for Management of Anti-Retroviral Therapies; see “Open Clinical Trials” on page 48), the study aims to address two critical questions: 1) Should treatment begin early, or should it depend on an individual’s risk of complications from HIV disease? and 2) Should treatment be continuous, or can it be interrupted based on improvements in the individual’s immune system?

In its first year, the SMART study will enroll 1,000 HIV positive people who will be randomly assigned to either a “go slow” (drug conservation) or a “hit hard, hit early” (viral suppression) treatment strategy. Participants in the “hit hard, hit early” arm will take antiretroviral therapy to suppress HIV levels to low or undetectable levels and will change regimens if their viral load is not adequately controlled. This approach is the one that many U.S. physicians currently use in treating people with HIV.

Participants in the “go slow” arm will agree not to take anti-HIV drugs unless their CD4 cell counts drop below 250 cells/mm<sup>3</sup>. They will then take medication only until their CD4 cell counts rebound above 350 cells/mm<sup>3</sup>. When on treatment, participants will be allowed to use any combination of FDA-approved antiretroviral agents.

If the investigators’ evaluation of the study’s long-term feasibility after one year is favorable, an additional 5,000 people will be enrolled over the following three years.

SMART will compare two distinct treatment strategies and will be the first study to examine the effectiveness and toxicity of various anti-HIV therapies over a prolonged period. While most HIV treatment trials measure indirect markers of disease progression, such as viral load or

CD4 cell count, SMART will measure actual clinical events, such as progression to an AIDS diagnosis or death, that develop only over a longer time. In addition, SMART will include several substudies to examine, for example, the effects of antiretroviral treatment on subjects’ cardiovascular health, changes in body fat distribution, and bone density.

## HOPS and Other Data

As the debate about the optimum time to initiate therapy goes forward, however, people with HIV and their providers cannot wait to make critical decisions. Several studies have looked into how individuals have fared when starting anti-HIV therapy at relatively high CD4 cell levels or when delaying treatment.

Some of the most important information available on all kinds of HIV treatment issues comes from the HIV Outpatient Study (HOPS). HOPS is a study of some 7,000 people with HIV at key treatment centers across the U.S. Begun in 1994, HOPS collects and analyzes data about these individuals’ treatment regimens, outcomes, adverse events, survival rates, and other information.

In a presentation at the 9<sup>th</sup> Conference on Retroviruses and Opportunistic Infections in February 2002, Frank J. Palella, MD, of Northwestern University in Chicago and colleagues compared data on the CD4 cell counts of 768 HOPS subjects from three different groups before they began antiretroviral therapy and the rate of death in each group. The three groups had 201–350, 351–500, and 501–750 CD4 cells/mm<sup>3</sup>, respectively. From their analysis of these data, the researchers concluded that starting therapy when the CD4 count is between 201 and 350 cells/mm<sup>3</sup>, and possibly even when it is between 351 and 500, is associated with reduced rates of death.

HOPS data also provide valuable information about another aspect of the relationship between CD4 cell count and the start of therapy.

Specifically, the occurrence of serious side effects associated with anti-HIV medications is lower in individuals who begin treatment at relatively high CD4 cell levels. HOPS data indicate, for example, that people who begin therapy at lower CD4 cell counts experience significantly higher rates of peripheral neuropathy and lipoatrophy (fat loss). Other studies have shown that starting therapy at a lower CD4 cell level is associated with an increased risk of developing resistance to antiretroviral medications and, as a consequence, treatment failure.

In contrast, a similar survey of 1,130 HIV positive subjects at the Johns Hopkins University clinic in Baltimore led researchers to conclude that therapy may be started at CD4 cell counts considerably lower than 350 cells/mm<sup>3</sup> without increased risk of new OIs or death, provided that the individual subsequently achieves durable control of HIV (long-lasting undetectable viral load). However, it is difficult to predict whether an individual will maintain durable HIV control, which depends on several factors such as medication adherence.

## Functional Immunity

A study published in the September 26, 2003 edition of *AIDS* tried to answer the question of whether delaying the initiation of HAART compromises the restoration of functional immunity in people whose CD4 cell counts returned to normal levels after effective therapy. In an HIV context, functional immunity refers to the immune system’s ability to fight OIs and to generate good antibody or cellular responses to vaccinations. Cristoph G. Lange, MD, from Case Western Reserve University in Cleveland and colleagues compared specific immune responses to certain immunizations such as tetanus and diphtheria in 29 HIV positive and nine HIV negative subjects. The HIV positive participants had started therapy at various CD4 cell nadirs (the lowest level ever reached), but all had achieved viral loads below 400

copies/mL and CD4 cell counts of at least 450 cells/mm<sup>3</sup> for a prolonged period. The researchers' analysis showed that there was a direct relationship between a person's CD4 cell nadir at the time antiretroviral treatment was started and that individual's production of adequate immune responses to the immunizations. (Response to tetanus and diphtheria vaccines, however, likely involved "memory" CD4 cells as opposed to "naive" CD4 cells. See discussion of the two cell types below.)

The study team concluded, "Delaying the initiation of HAART in chronic HIV-1 infection results in impaired functional immune restoration despite normalization of circulating CD4 T cell numbers.... Our results suggest that, even when CD4 T cell counts have 'normalized,' prior immune decline determines current immune competence.... Our data demonstrate that, even in those persons who normalize CD4 T cell numbers and are largely protected from opportunistic infection, immune deficits persist." (T cells are white blood cells that carry out the cell-mediated immune response.)

### Treatment-naive people with less than 500 CD4 cells/mm<sup>3</sup>

Similar studies also seem to suggest that starting treatment earlier, when the CD4 cell count is higher, can preserve important aspects of immune system function. In a study published in March of this year in *HIV Medicine*, Lena al-Harhi, PhD, of Rush-Presbyterian-St. Luke's Medical Center in Chicago and colleagues examined the effects of HAART on a number of specific markers of immune system function in 13 antiretroviral-naive individuals.

All study participants had CD4 cell counts below 500 cells/mm<sup>3</sup> and had never taken anti-HIV medications. The researchers administered a regimen of 3TC (lamivudine, Epivir), abacavir (Ziagen), and amprenavir (Agenerase) twice daily and followed the subjects for 48 weeks. At the start of the study, the participants' median CD4 cell count was 207 cells/mm<sup>3</sup>;

after 48 weeks, the median count had increased to 617 cells/mm<sup>3</sup>. (The median is the middle value in an entire range of values.)

The researchers examined the effects of HAART on several HIV-specific immune responses. HIV-specific immune responses refer to, among other things, the extent of the expression of particular marker molecules on the surface of each individual's CD4 cells (which coordinate immune system activity) and CD8 cells (which regulate immune responses or actively destroy virus-infected cells), as well as the total numbers and ratios of those cells in relation to each other. The study results were then interpreted as indicators of the extent to which the participants' immune systems had recovered "normal" functionality.

Al-Harhi's team found that while individuals receiving HAART generally experience substantial viral load decreases, their immune responses often do not normalize. In this study, plasma viral load sharply declined within four weeks after the start of therapy and fell below the detection limit of 50 copies/mL for the majority of participants by week 16. Although the median CD4 cell increase was substantial, it consisted predominantly of memory cells. The number of naive CD4 cells did increase, but much more slowly and to a lesser extent than memory cells. This is critical in terms of functional immunity, because memory CD4 cells have receptors only for foreign antigens encountered during past infections or vaccinations. Naive CD4 cells, in contrast, respond to antigens that the immune system has not processed before, such as those associated with a new opportunistic infection. When naive CD4 cells are activated and proliferate, they create an acquired immune response to the newly encountered pathogen. Naive CD4 cells are therefore highly desirable in those taking anti-HIV therapy.

It is also important that HAART lead to the production of functional immune cells. One measurement of functionality is called the lymphoproliferative assay (LPA). The LPA

measures the lymphoproliferative response, or the rapid replication of T cells when exposed to certain disease-causing agents. Al-Harhi's research group tested participants' responses to *Candida* (a yeast-like fungus associated with candidiasis, or thrush), cytomegalovirus (CMV, a herpesvirus), and *Mycobacterium avium* (bacteria associated with *Mycobacterium avium* complex, or MAC). One of the 13 individuals recovered a response to *Candida* that was maintained until week 48. At baseline, five of the 13 participants had *Candida* responses, which declined by week 48. One subject recovered a CMV response, and another gained it briefly. CMV responses were present at baseline for six subjects, but by week 48 they also had declined. Two participants recovered a *Mycobacterium* response, and another did so for short time; two others maintained their initial response, while the remainder had no *Mycobacterium* response at baseline.

The authors maintained that the timing of HAART initiation in antiretroviral-naive individuals shows a clear distinction between starting treatment above and starting treatment below a CD4 cell count of 500 cells/mm<sup>3</sup>. By focusing closely on specific aspects of immune system reconstitution (such as an increased number of functional CD4 cells), they advised that "intervention prior to CD4 T cell decline below 500 cells/mm<sup>3</sup> is of greater benefit to the patients." The researchers concluded that, although "recent treatment guidelines have recommended HAART initiation at 350 cells/mm<sup>3</sup>...the level of immune restoration, based on HAART alone, is greater when the treatment is initiated with CD4 counts above 500 cells/mm<sup>3</sup>."

### Treatment-naive people with more than 500 CD4 cells/mm<sup>3</sup>

Controlled studies of immune restoration in treatment-naive individuals who began HAART at CD4 cell levels above 500 cells/mm<sup>3</sup> are very few in number. In a study published in the May 5, 2000 edition of *AIDS*, al-Harhi and colleagues assessed

## HIV SPECIALISTS GENERALLY AGREE

### CD4 CELLS VS VIRAL LOAD

that a person's CD4 cell count should be the key factor to consider when deciding whether and when to begin a HAART regimen, with viral load playing a secondary role. Once an individual begins HAART, however, the priorities of these two factors reverse, with viral load receiving greater consideration in determining the success or failure of a treatment regimen.

The viral load test is essential in managing anti-HIV therapy because it is the one tool that clearly indicates whether antiviral medications are working properly, as each of them (except for the entry inhibitors, such as T-20 [enfuvirtide, Fuzeon]) is designed to directly inhibit the virus' ability to replicate. Changes in the CD4 cell count, as they follow declines or increases in the viral load, provide secondary indicators.

Notably, even people for whom HAART has successfully controlled HIV replication for some time can experience occasional blips (small, transient increases) in their viral load. A blip is normally considered to occur when a suppressed viral load rises above 50 copies/mL and is followed by a measurement below 50 copies/mL on the next test. Several circumstances may explain viral blips, including variations in drug concentrations in the blood over time; immune activation due to other acute, active infections, such as influenza or herpes; immune system stimulation following certain vaccinations; and laboratory error in measuring the viral load. Regular viral load monitoring allows caregivers to distinguish such fairly common blips from a HAART regimen's failure to suppress viral replication.

immune function in early HIV disease in 17 individuals with a median CD4 cell count of 550 cells/mm<sup>3</sup>, which increased to a median of 800 cells/mm<sup>3</sup> over the 48 weeks of the study. The key markers of T cell activation (HLA-DR and CD38) and the apoptosis marker CD95 were significantly reduced. CD4 memory cells increased from a median of 323 to 386 cells/mm<sup>3</sup>, but, more importantly, naive CD4 cells increased even more—from a median of 202 to 318 cells/mm<sup>3</sup>.

The researchers assessed participants' lymphoproliferative responses to the pathogens *Candida* and tetanus. At baseline all patients showed responses to *Candida*, which were maintained for the 48 weeks of the study. For tetanus, 88% of participants were responsive at study entry, and that rate increased to 100%. The authors concluded that "viral suppression in early disease may lead to a better immunological reconstitution outcome than in late HIV disease, where alternative immune reconstitution strategies may be the best

option in conjunction with potent HIV suppression to restore immunity in advanced HIV disease."

### Cost-Effectiveness of Early Treatment

A study presented at the 1<sup>st</sup> International AIDS Society Conference on HIV Pathogenesis and Treatment in 2001 reported that the greater drug costs associated with early treatment were offset by reduced non-drug-related costs of caring for people with HIV. Study authors Teresa Kauf, PhD, of Duke University in Durham and colleagues examined the total treatment costs of 768 antiretroviral-naive HIV positive individuals in three cohorts, based on their baseline CD4 cell counts: those with less than 350, those with 350–500, and those with more than 500 CD4 cells/mm<sup>3</sup>. After adjusting costs to 1999 U.S. dollars and accounting for typical life expectancies, they determined the

total lifetime costs of HIV care for the three cohorts to be \$185,442; \$163,246; and \$137,910, respectively.

### Going Round the Table

In September 2003 a scientific roundtable meeting was convened in Atlanta by GlaxoSmithKline "to consider optimal time points and criteria for initiating HAART in patients with chronic asymptomatic HIV infection." Participants reviewed most of the major studies, drawing heavily on HOPS, as well as the NIH guidelines. There was considerable discussion of the importance of considering CD4 cell nadir when deciding whether to start therapy. Participating clinicians and researchers discussed arguments on both sides of the early vs late treatment debate.

The roundtable did not come down firmly on either side of the "go slow" vs "hit hard, hit early" debate. But participants emphasized the importance of identifying individual

factors in determining an HIV treatment strategy. These factors could include age, comorbid conditions such as hepatitis C or cardiovascular disease, the likelihood of poor adherence, recreational drug use, pregnancy, and the individual's daily schedule and lifestyle needs.

The chairman, Martin S. Hirsch, MD, of Harvard Medical School in Boston optimistically suggested that ongoing developments may help to clarify concerns over whether treatment should begin at a CD4 cell count of 200, 350, or higher: "New drugs and refined approaches to therapy continue to yield improvements in terms of adherence, risk for treatment failure, and adverse effects. It is likely that as treatment regimens improve with respect to potency and tolerability, the pendulum will switch towards earlier therapy." Although the participants were careful to consider both sides of the question thoroughly, the chairman's report on the meeting seems to strongly suggest that treating an individual relatively early in the course of HIV infection should always be given serious consideration.

## Reluctance to Start Therapy

As another complicating factor, some HIV positive people refrain from taking anti-HIV medication regardless of recommendations. The reasons for this can be as complex as the course of HIV disease itself.

For some individuals, a reluctance to begin HAART may stem from a disconnect between the normal health and vitality they feel and the continuous damage to the immune system that HIV infection causes, even when that damage is evident in the person's lab results. Often, only the occurrence of one of the early symptoms associated with HIV disease progression, such as thrush, persistent fever, or swollen lymph nodes, ultimately convinces them of the need to start anti-HIV therapy. Other reasons for refusing therapy might include an unwillingness to embark on a life-long course of treatment, an aversion to the strict requirements of HAART or to allopathic (Western) medicine in general, or not wanting to be reminded

of one's HIV illness. Cultural barriers or access issues may discourage some people from beginning treatment. Discussions with care-givers, family, or friends may be helpful in underscoring the benefits of antiretroviral therapy and in solving problems of access or acceptance in many of these cases.

The possibility of experiencing visible body shape changes, or lipodystrophy, also leads some people to decline to take anti-HIV therapy. (Metabolic complications associated with lipodystrophy, such as insulin resistance and high blood lipid levels, are not visible and may be perceived as less threatening in the short term.) Although fat accumulation and fat loss do not generally pose serious risks to physical health, they may be easily seen and may cause physical discomfort or pain, as well as considerable emotional and social problems. For example, lipoatrophy can cause the face to take on a sunken, gaunt appearance, which for many people is a clear sign of their positive HIV status. The condition seems to be associated with certain drugs, particularly

## THE EXPERIENCE GAINED FROM TREATING OTHER CHRONIC

### CHIEF CONSIDERATIONS

health conditions such as diabetes, arthritis, and heart disease offers valuable lessons concerning HIV treatment strategies. One lesson that can be drawn from the treatment of such conditions is the importance of not waiting until irreversible damage has developed before starting therapy. Another is the multifactorial nature of critical treatment decisions. Since a single factor rarely determines the entire course of a disease, HIV positive people and their providers must consider several issues when deciding whether to start or to delay anti-HIV treatment:

**CD4 cell count**—not only the current level but also the trend in the rate of decrease.

**Clinical status**—such as whether the individual shows symptoms associated with HIV disease progression or is pregnant.

**Adherence**—the individual's ability to use anti-HIV medications as directed and adapt to the demands of long-term drug therapy.

The individual should also consider his or her clinician's experience in managing other people with HIV. Controlled studies have shown that individuals treated by physicians who have extensive experience with other HIV patients have significantly better clinical outcomes. No less important, the person with HIV should have a trusting and communicative relationship with his or her clinician. If not, switching to another provider may be advantageous.

d4T (stavudine, Zerit). Some of the manifestations of fat accumulation may lead to problems beyond concerns about appearance. A dorso-cervical fat pad (“buffalo hump”) may cause headaches and problems with sleeping or breathing. Enlarged breasts in women can be a painful condition. Due to their change in body image, people with body fat irregularities may also experience depression, social withdrawal, anxiety, and low self-esteem. The possibility that any of these conditions could occur is one of the most often cited reasons HIV positive individuals give for delaying the start of treatment.

Encouragingly, HIV management strategies and specific treatments that can help people avoid or minimize lipodystrophy are becoming available and increasingly widely used. Management strategies include switching to a PI—such as the recently approved atazanavir (Reyataz)—that does not seem to be associated with a significant incidence of lipodystrophy, or using a HAART regimen based on a non-nucleoside reverse transcriptase inhibitor (NNRTI) such as efavirenz (Sustiva) or nevirapine (Viramune), rather than a PI. Switching from a NRTI such as d4T to another less associated with lipodystrophy is another option. Increased exercise, both aerobic and strength training, may lead to body fat improvements, as might greater attention to diet.

Specific treatments for body shape changes are being used, although not all are equally effective. A liquid preparation of polylactic acid (Sculptra, New-Fill) can be injected under the skin of the cheeks to stimulate collagen production and significantly improve the appearance of sunken cheeks. (See “News Briefs,” page 6 in this issue, and “New-Fill to Treat Facial Wasting,” *BETA*, Spring 2002.) Certain medications, such as human growth hormone or testosterone supplements, have shown some efficacy in reducing fat accumulation and promoting muscle growth. (See “HIV and Hormones,” page 34 in this issue, and

“The Many Faces of Human Growth Hormone,” *BETA*, Winter 2003.) Liposuction has been shown to be somewhat helpful in reducing or eliminating buffalo humps and, to a lesser extent, fat accumulation around the abdomen and in the breasts.

Concerns about adverse events such as body shape changes must be taken seriously in the context of the debate about the advantages of early vs delayed initiation of anti-HIV therapy. For those who are reluctant to undertake treatment, developing a clear understanding of the key issues is vital. First, lipodystrophy—with or without significant body shape changes—is not inevitable for everyone taking HAART. Lipodystrophy may be linked with other factors such as aging or HIV infection itself. Second, management and treatment options can help many people avoid or limit the problems of body shape changes.

## Looking Ahead

The direction of HIV drug development might overtake the debate about whether it is better to start or delay treatment. Several highly effective NNRTIs that lack some of the serious side effects and cross-resistance concerns of the currently available drugs in this class are well along in clinical trials. (Cross-resistance refers to drug resistance to more than one drug or to an entire class of drugs.) Unlike other PIs, atazanavir appears to have a minimal effect on lipids such as cholesterol and triglycerides, although long-term outcomes and the effects of ritonavir boosting are still unknown. In addition, the current trend in developing and prescribing antiretroviral agents is toward once daily and other simplified treatment options, which may positively address adherence concerns. Several anti-HIV drugs, such as efavirenz, atazanavir, and tenofovir DF (Viread) are now available in once-daily formulations, and others are expected to become available in the next few years.

Taken together, these trends seem to suggest that early treatment might again become the recommended approach in HIV therapy. With simpler regimens and drugs that are less associated with serious long-term adverse events, starting HIV treatment at higher CD4 cell levels may help preserve functional immunity, reduce concerns about side effects, and allow people with HIV to live long and productive lives.

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# ADAP in Peril

**HUNDREDS WAITING FOR AIDS DRUG ASSISTANCE IN COLORADO.**

**THREE PEOPLE WITH HIV/AIDS DIE WHILE ON WEST VIRGINIA ADAP WAITING LIST.**

**CALIFORNIA GOV. SCHWARZENEGGER'S BUDGET WOULD CAP ADAP ENROLLMENT.**

**NORTH CAROLINA AID FOR HIV WILL RUN SHORT: STATE TO PUT PEOPLE ON A WAITING LIST.**

These are just a few of the headlines that have been published in recent months in newspapers throughout the U.S. They tell a bleak story: a growing number of Americans living with HIV/AIDS are being denied access to HIV treatments, which can mean the difference between life and death. Sadly, this situation appears to be worsening and our national leaders have not shown the political will to solve the problem. How did we get to this point, and what can be done to rectify the situation?

Fred Dillon

## ANTI-HIV DRUGS: COSTS AND CONSEQUENCES

The introduction of highly active antiretroviral therapy (HAART) in 1996 created a revolution in HIV treatment that has resulted in major reductions in HIV-related morbidity and mortality. A study published in the October 18, 2003 edition of *The Lancet* found that HAART has reduced AIDS-related death rates by more than 80% and increased life expectancy for HIV positive people taking these drugs to more than ten years.

These treatments also come at a high price. The average cost of a year's supply of antiretroviral therapy is over \$12,000, a price that is well beyond the reach of low-income individuals and others who are uninsured or underinsured. Government programs have therefore been critical in ensuring access to these medications.

One of the most vital of these programs is the AIDS Drug Assistance Program (ADAP), which provides HIV-related drugs to those who otherwise could not afford them. This program is a lifeline for thousands of low-income people living with HIV/AIDS. For those who lack adequate health insurance and do not have access to other government programs such as Medicaid, ADAP is generally the only option available to obtain lifesaving anti-HIV medications.

### A BRIEF PRIMER ON ADAP

ADAP was established in 1987 as an emergency program to provide federal support to states to help provide drugs (especially the newly discovered AZT [zidovudine, Retrovir]) to individuals living with HIV/AIDS who could not otherwise afford these treatments. This drug access program was incorporated into Title II of the Ryan White CARE Act, which was passed in 1990.

ADAPs exist in all 50 states, the District of Columbia, and six other American territories and associated jurisdictions. The program is designed to pay for HIV-related treatments for people with HIV/AIDS who do not have adequate insurance coverage. It

covers those who are not eligible for Medicaid and lack adequate private health insurance. Like other Ryan White CARE programs, ADAP serves as the payer of last resort, meaning that the program is accessed only if no other option exists for paying for these drugs.

Each state administers its own ADAP and, under the CARE Act, states are given wide latitude over the specific nature of the program. States control decisions about which drugs are covered by the program (the formulary) as well as the eligibility requirements and administrative procedures. As a result, ADAPs vary tremendously from state to state. Financial eligibility requirements range from 125% of the federal poverty level in some states to 400% or more of the federal poverty level in others. In 2003 the number of drugs covered by different ADAPs ranged from 18 to 474.

While ADAP is federally funded through Title II of the Ryan White CARE Act, the majority of states also contribute their own resources to augment these federal dollars. Thirty-six states contributed funds to their ADAPs in 2002.

It is estimated that ADAPs served 136,000 unduplicated clients in 2003, representing about 30% of people living with HIV/AIDS who are receiving HIV care in the U.S. The National ADAP Monitoring Project found that ADAPs served more than 85,000 clients during a single month, June 2003. Most of these clients are low income (over 80% are at or below 200% of the federal poverty level) and a majority (60%) are people of color.

### MOUNTING PRESSURE

Funding for ADAP has not kept pace with the growth in the demand for the program. The need for ADAP is driven by three key factors: 1) the number of people living with HIV in the country who are eligible for the program, 2) the number and types of drugs needed by ADAP participants, and 3) the price of the drugs prescribed. All three factors have

increased dramatically over the years and continue to move upwards.

Because of the treatments now available, people with HIV/AIDS are living longer than ever before. This, however, has meant that there is a growing number of people living with the disease who need treatment and services. The National ADAP Monitoring Project estimated that the number of ADAP clients grew by 154% between 1996 and 2002. At the same time, combination therapy has grown more complex, with many people shifting from triple-drug regimens to combinations that include four or more drugs.

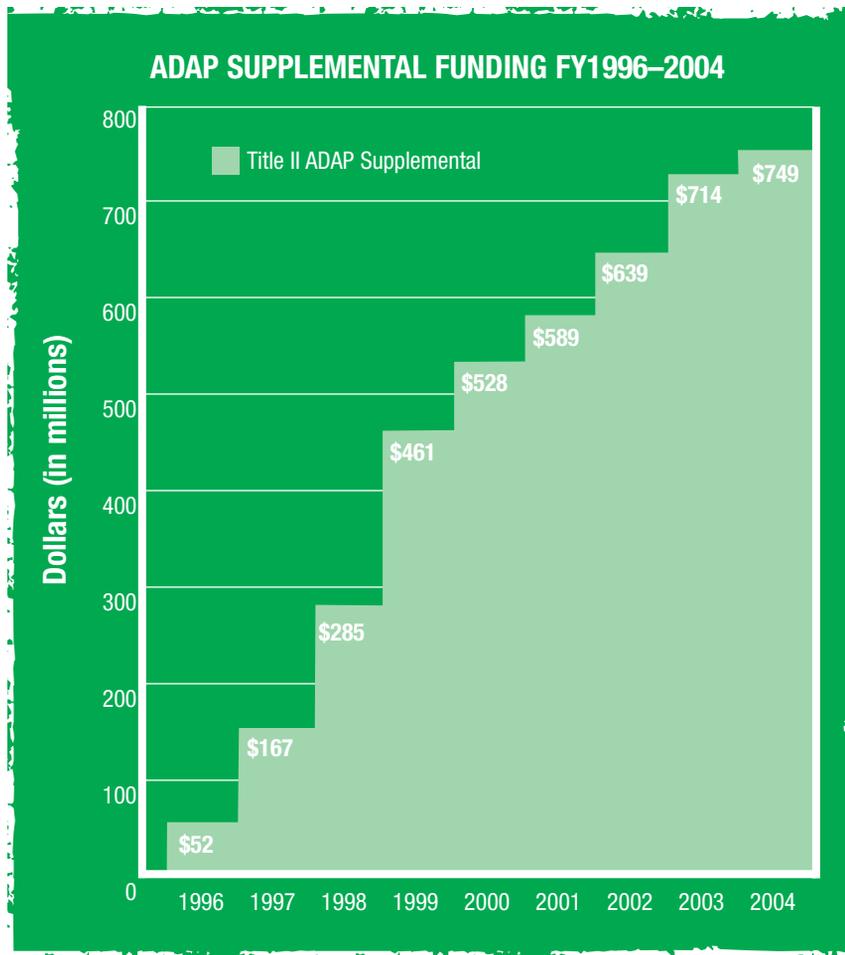
Rising prescription drug costs have also played a role in straining ADAP budgets. During some recent years, price hikes have consumed most of the modest funding increases advocates have been able to obtain at the federal level. This has left little funding available to cover the growing number of people who are eligible for the program.

Several years ago, as the ADAP crisis started to escalate, several pharmaceutical manufacturers, led by Pfizer, Inc., agreed to freeze their prices for drugs administered through ADAP. Most companies have recently abandoned this commitment and have again begun to impose significant price increases. For example, GlaxoSmithKline (GSK) instituted a 4.9% increase on all of its pharmaceuticals in January of this year, and ADAP was not spared from this price hike. Similarly, Boehringer Ingelheim added a 4.5% increase to nevirapine (Viramune), a non-nucleoside reverse transcriptase inhibitor (NNRTI), the same month. And Bristol-Myers Squibb (BMS) added a 4.8% price increase to various drugs in March, the second price hike in less than seven months. The cost of BMS's atazanavir (Reyataz), a protease inhibitor (PI), is now 9.2% higher than it was when the drug was approved in August 2003. The cost of GSK's fosamprenavir (Lexiva), another new PI, is now 9.3% higher than when it was approved in November 2003.

In another stunning development, Abbott recently raised the price of ritonavir (Norvir) by 400% (see related story on page 15). Although the company has promised not to apply this increase to ADAPs, the price hike will inevitably drive up the cost of providing HIV care. The health insurance industry is likely to pass on the higher costs that result from this price increase in the form of higher premiums and co-pays. Not only will this increase the burden on individuals who are already struggling to meet rocketing cost-sharing obligations, but it will also almost certainly force more people to turn to public programs, such as ADAP and Medicaid, for assistance. In addition, those ADAPs that cover private co-pays or premiums for people who cannot afford them (allowing these individuals to stay in the private health care system) could experience an immediate negative impact. Furthermore, Abbott has not committed to maintain the lower price for ADAPs in the event that ritonavir is reformulated. ADAPs will therefore be at great risk of having to pay much higher prices for a newer version of the drug, placing further financial strain on these programs.

## FEDERAL FUNDING FALLS SHORT

As these pressures on ADAP have escalated, federal funding has remained stagnant. ADAP funding has never been sufficient to meet the needs across the country, but in recent years the gap between the need and actual funding levels has ballooned into hundreds of millions of dollars. In fiscal year (FY) 2004, it was estimated that \$214 million in additional funding was needed to meet the needs of those eligible for the program, but the final increase provided totaled a mere \$35 million. For FY2005, AIDS treatment experts estimate that an additional \$217 million will be needed to maintain access to anti-HIV medications and minimize limitations on state ADAPs. But President George W. Bush's budget includes only a \$35 million increase.



Why have funding increases for ADAP become so difficult to obtain in recent years? In reality, all HIV/AIDS programs (and many other health-related programs) have been severely underfunded in recent years. President Bush and his administration have not prioritized domestic AIDS issues since taking office in 2000. In fact, Bush was the first president to propose flat funding for the Ryan White CARE Act, which funds ADAP and a range of other HIV care programs. The president's budget flat-funded these programs in both FY2001 and 2002, and provided only a slight increase for ADAP in both FY2003 and 2004.

President Bush and Congress have had other priorities. In particular, the push for substantial tax cuts severely restricted the dollars available to fund critical health programs, including HIV/AIDS programs. The national economic downturn has also resulted in significant reductions to

the federal treasury. And, after the events of September 11, 2001, spending on "homeland security" and the "war on terror"—including the military campaigns in Afghanistan and Iraq—increased dramatically, leaving little additional revenue available for other important priorities. As a result of tax cuts and soaring defense expenditures, the federal deficit will reach nearly \$500 billion this fiscal year, placing enormous pressure on Congress to reel in spending.

As a result of all of these factors, it is extremely difficult for advocates at the federal level to do anything more than protect existing funding for most HIV programs while securing incremental and extremely insufficient increases for ADAP. Worse yet, state governments have also faced massive budget deficits due to the weak economy, which has hampered states' ability to make up for shortfalls at the federal level.

# Federal ADAP Funding

Before FY1996, ADAP did not have an independent budget line item. States individually determined what portion (if any) of their Title II CARE Act funding would be used for ADAP and combined this with state resources, if they provided any state-specific funding for the program, and, in some jurisdictions, with other federal CARE Act dollars.

In FY1996, due to the fiscal pressures related to combination therapy, President Bill Clinton and Congress agreed to appropriate \$52 million specifically for ADAP. Often referred to as the "ADAP Supplemental," this specific federal funding grew markedly for several years due to increasing demand for the life-saving combination HIV/AIDS therapies that were brought to market during this period. (See chart on previous page.) In recent years, the growth of funding for all portions of the CARE Act has slowed and ADAP appropriations have been far short of the funding levels needed for the program.

## STATES RESPOND BY RESTRICTING ACCESS

As a result of this funding crisis, many states have had to impose harsh restrictions on their ADAP programs. These measures have included capping enrollment, tightening financial eligibility criteria, putting individuals who need drugs on waiting lists, instituting per capita expenditure limits, restricting access to certain drugs, and/or dramatically reducing the number of drugs available through program formularies. Such changes have resulted in reduced access to anti-HIV drugs for many people living with the disease.

The number of states imposing such restrictions, and the number of people affected, is growing. A review of state programs in May 2004 found that 1,545 individuals were on ADAP waiting lists throughout the country, a startling increase from the 791 individuals who were on waiting lists as of January 2004.

The May review also found that 14 states, including Alabama, Colorado, North Carolina, and Washington, had

implemented at least one or more program restrictions due to a lack of sufficient resources. At least ten other states, including California, New Jersey, and Texas, may impose new or additional restrictions during FY2004.

These waiting lists have meant that hundreds of people are being denied access to life-saving HIV drugs. Several people have reportedly died while waiting to enter the program. The situation appears to be growing worse, and more lives are being put at risk as a result.

It should also be noted that while waiting lists provide one indicator of the unmet need for ADAP services, they do not reflect the full level of need for the program. Some people who receive medications through ADAP may not be given as much treatment as they require, particularly in states with limited drug formularies.

## HOW TO ADDRESS THIS CRISIS?

There are several options for ensuring access to anti-HIV drugs throughout the U.S. Some can be

accomplished quickly, while others require a long-term strategy. Each of these avenues must be pursued aggressively to assure broad access to HIV/AIDS therapies now and in the future.

### ***Increase Funding for ADAP***

The immediate and obvious solution would be a major infusion of federal dollars for ADAP. Federal AIDS advocates are pushing hard to significantly increase ADAP funding in both the current and the coming fiscal year. Key members of Congress and AIDS advocates are pushing for an emergency appropriation of \$122 million in additional resources for ADAP in FY2004, as well as the needed increase of \$217 million for FY2005.

Given the federal budget deficit and the competing priorities discussed above, it remains unclear how successful these efforts will be. Members of Congress and the administration need to hear an outpouring of support from people throughout the country about the importance of these funding requests. Unless constituents implore their members of Congress to address this issue, it is unlikely that significant funding increases will be obtained anytime soon.

### ***Get the Best Price***

The other logical way of reducing costs and stretching available ADAP dollars is to minimize the costs of HIV treatment. As noted previously, many anti-HIV drugs used in combination regimens are extremely expensive and prices for these medications continue to rise.

As access to HIV treatment is increasingly threatened and denied, the AIDS community must rely on its pharmaceutical industry partners to exercise restraint in profit-making. Significant price increases, such as the massive hike for ritonavir, are unjustifiable and severely limit the ability to ensure access to HIV care for all those in need. The industry must be urged to rein in prices for HIV medications to ensure broad access to these drugs.

Another option related to drug pricing is to secure additional rebates



## California Advocates Prevent Cutbacks

**T**he ADAP crisis has been felt keenly in California. For the first time, the state government proposed major limits to the program, which could have resulted in anti-HIV drugs being denied to thousands of Californians living with the disease.

In December 2003, as part of a package of \$1.9 billion in cuts he hoped to make mid-way through the 2003–2004 budget year to address a massive state deficit, Governor Arnold Schwarzenegger proposed that enrollment in ADAP be permanently capped at its current level of 23,900 enrollees. While about 300 ADAP clients leave the program each month and could be replaced with new enrollees, it is estimated that the governor's proposal would result in approximately 120 people being placed on a waiting list for anti-HIV medications every month. Fortunately, the legislature did not act on the governor's mid-year ADAP proposal and the program has not been capped at this time.

In January 2004 Governor Schwarzenegger released his first state budget proposal in the face of an alarming state deficit of \$14 billion. Although his draft budget for FY2004–2005 did not contain significant cuts to state HIV/AIDS services, Schwarzenegger failed to provide additional funds needed to assure full access to California's ADAP and again proposed a cap on enrollment in the program.

The governor's FY2004–2005 budget proposal includes \$207 million for ADAP, including federal and state funds as well as rebates from pharmaceutical companies. Each year for the past several years, California's ADAP has received increased funding to meet annual growth in enrollment, increased usage of drugs by clients, and rising drug prices. For FY2004–2005, ADAP needs to be funded at \$232 million—an increase of \$25 million over the governor's budget proposal—to prevent the imposition of a waiting list.

Fortunately, ADAP advocates in California mobilized aggressively to secure adequate funding for this life-saving program and stave off an enrollment cap. Over 700 people with HIV/AIDS and their supporters traveled to the state capital on March 8, 2004, to demonstrate against an ADAP waiting list and in favor of additional funding for ADAP.

That same day the Senate Budget Subcommittee on Health responded to the pleas of ADAP clients and advocates. First, the subcommittee approved some minor changes to the program that reduced spending by \$800,000 and used that money to offset the \$500,000 the governor said would be saved by capping ADAP enrollment. To cheers from ADAP advocates in the packed hearing room, the subcommittee then affirmatively rejected the enrollment cap. The subcommittee also acknowledged that ADAP has accumulated \$21 million from rebates paid by pharmaceutical companies on its purchases. It allocated \$15 million of that amount to ADAP and used the remaining \$6 million to help address the state's budget deficit. Advocates were confident there would be \$10 million in additional rebate money available during the coming budget year to assure that California's ADAP has all the funds it needs.

In response to the community's demands and the legislature's actions, Governor Schwarzenegger recently agreed to include \$27 million in additional funding for ADAP in his revised budget proposal, which was released on May 13. This prevents an enrollment cap in California and assures unlimited access to medications for people now in the program for the coming fiscal year.

*BETA* readers who would like more information about California's ADAP or who want to join in ADAP advocacy should contact Dana Van Gorder at 415-487-3099 or sign up for the San Francisco AIDS Foundation's HIV Advocacy Network (HAN) at [www.sfaf.org](http://www.sfaf.org).

# The ADAP Watch

AIDS Drug Assistance Programs (ADAPs) provide life-saving HIV treatments to low income, uninsured, and underinsured individuals living with HIV/AIDS in all 50 states, the District of Columbia, the Commonwealth of Puerto Rico, the U.S. Virgin Islands, three U.S. Pacific Territories (Guam, the Commonwealth of the Northern Mariana Islands, and American Samoa), and one Associated Jurisdiction (the Republic of the Marshall Islands). Federal funding for ADAPs in FY2003 and FY2004 has been insufficient to meet the needs of those eligible and has led to ADAP access restrictions. Eleven ADAPs have a current waiting list. As of May 14, 2004, there were 1,545 individuals on ADAP waiting lists nationwide. Six ADAPs have instituted capped enrollment and/or other cost-containment measures since April 2003. Ten states anticipate the need to implement new or additional program restrictions during FY2004, which ends March 31, 2005.

## ADAPs with waiting lists\* (as of May 14, 2004)

**Alabama:** 351 on waiting list (FY1999)  
**Alaska:** 9 on waiting list (FY2003)  
**Arkansas:** 1 on waiting list (FY2004)  
**Colorado:** 297 on waiting list (FY2003)  
**Idaho:** 5 on waiting list (FY2000)  
**Iowa:** 3 on waiting list (FY2004)  
**Kentucky:** 113 on waiting list (FY2002)  
**Montana:** 4 on waiting list (FY2002)  
**North Carolina:** 685 on waiting list (FY2001)  
**South Dakota:** 43 on waiting list (FY2000)  
**West Virginia:** 34 on waiting list (FY2002)

\* Fiscal year in parentheses indicates when waiting list was initially instituted

## ADAPs with other cost-containment strategies in place

**Colorado:** reduced formulary  
**Idaho:** monthly expenditure cap  
**Indiana:** capped enrollment  
**Oklahoma:** reduced formulary and annual expenditure cap  
**South Dakota:** annual expenditure cap  
**Washington:** increased and expanded cost-sharing (effective 4/1/2004)

## ADAPs anticipating new/additional restrictions during FY2004

Alabama	New Jersey
California	New Mexico
Massachusetts	Oregon
Missouri	South Carolina
New Hampshire	Texas

Adapted from NASTAD, a non-profit national association of state health department HIV/AIDS program directors who have programmatic responsibility for administering HIV/AIDS health care, prevention, education, and supportive services programs funded by state and federal governments. If you would like to receive The ADAP Watch, please send your e-mail address to Beth Perry at [bcrutsinger-perry@nastad.org](mailto:bcrutsinger-perry@nastad.org).

and/or price reductions from pharmaceutical manufacturers to help support ADAP. In 2003 the ADAP Crisis Task Force of the National Association of State and Territorial AIDS Directors (NASTAD) was successful in reaching agreements with all eight of the major pharmaceutical companies that manufacture antiretrovirals to provide financial relief for ADAP. Annual savings from these agreements were estimated

to be between \$60 and \$65 million, and helped many states avoid imposing additional restrictions on their programs.

## Reform Entitlement Programs

The Ryan White CARE Act as a whole is a discretionary program that must be specifically funded every year by Congress through the appropriations process. There is no guaran-

tee from year to year that sufficient funding will be provided. In contrast, entitlement programs, such as Medicaid (the health insurance program for low-income Americans), are essentially guaranteed every year. These programs are not reliant on the annual appropriations process and are assured to be available unless Congress changes the law. Ensuring that additional people with HIV are covered by entitlement programs would help ensure access to HIV care from year to year and would take significant burdens off of ADAP and other discretionary programs.

Current eligibility guidelines restrict access to Medicaid for many low-income people living with HIV. Because Social Security Administration regulations do not define individuals with early HIV infection as “disabled,” the majority of low-income Americans with HIV are ineligible for Medicaid and are unable to receive HIV-related drugs and health care through the program. Medicaid regulations should be amended so that “disability” for the purposes of program eligibility is defined as “HIV disease” and applies to low-income individuals throughout the spectrum of disease.

Medicaid guidelines are clearly out of step with current medical science and standards of care. U.S. Public Health Service guidelines call for medical care early in the course of HIV infection, before symptoms of AIDS have developed. Early HIV care has been shown to reduce expensive hospital stays, allow people to remain at work, and prolong and improve individuals' lives.

If Medicaid is not reformed to serve people early in the course of HIV infection on a national scale, then the federal government should at least facilitate state efforts to expand the program. The Early Treatment for HIV Act (ETHA) is a bipartisan piece of legislation introduced by Congresswoman Nancy Pelosi (D-CA) and Congressman James Leach (R-IA) in the House (H.R. 3859) and by Senators Gordon Smith (R-OR) and Hilary Rodham Clinton (D-NY) in the

Senate (S. 847). ETHA would give states the option to expand their Medicaid programs to cover people early in the course of HIV disease without having to apply for a federal waiver. It is modeled after the successful Breast and Cervical Cancer Prevention and Treatment Act of 2000, which allows states to provide early intervention Medicaid access to women with breast and cervical cancer.

Unfortunately, the current political and fiscal environment in Washington has not been conducive to the passage of ETHA. Instead, the focus in recent years has been on scaling back the Medicaid program. While Medicaid champions in Congress have thus far been able to stall attempts to block grant (disperse funds in a lump sum) and/or significantly reduce funding, threats to the program continue. As a result of these factors, ETHA has been introduced for several years but has not moved forward. Advocates and constituents must continue to exert tremendous pressure on their members of Congress about the importance of this legislation, as well as the ongoing need to maintain the existing Medicaid program.

An additional option was recently proposed in a report by a National Academy of Sciences Institute of Medicine (IOM) panel. The report, entitled "Public Financing and Delivery of HIV/AIDS Care: Securing the Legacy of Ryan White," calls for the establishment of a new federal entitlement program designed specifically to provide HIV care and treatment to low-income Americans without adequate access to health insurance. The proposed program would create a national standard of care, including consistent nationwide eligibility requirements and a federally defined list of services. The IOM report explained that this is the best approach to "address gaps and a lack of coordination" in the current system.

Advocates strongly support the IOM's conclusion that "failing to provide these cost-effective, life-saving drugs to all Americans who need them—including individuals who lack

insurance or cannot afford them—is indefensible." Yet the bold call for entitlement coverage for low-income people with HIV is unlikely to be embraced by a federal government that is unwilling to provide sufficient resources to fully serve people who are currently seeking HIV care.

## UNIVERSAL HEALTH CARE: THE TRUE SOLUTION

In the long run, the true solution to gaps in medical care and prescription drug coverage for Americans living with HIV/AIDS is to ensure universal health care for all Americans. The U.S. is the only developed nation whose political leaders have not yet found a way to guarantee affordable access to comprehensive health care for all of its people. It is estimated that one in seven Americans—more than 40 million—lack health-care coverage, and among these individuals are people who currently rely on ADAP for their anti-HIV medications. ADAP is only a Band-Aid for addressing America's failing health-care system. The AIDS community must continue to work with other health advocates to push our country to ensure access to health care for everyone who needs it.

**Fred Dillon is deputy director of the Policy and Communications department of the San Francisco AIDS Foundation.**

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Porter, K. and others. Determinants of survival following HIV-1 seroconversion after the introduction of HAART. *The Lancet* 362(9392): 1267–1274. October 18, 2003.

*Public Financing and Delivery of HIV/AIDS Care: Securing the Legacy of Ryan White.* The National Academies Press. [www.nap.edu/books/0309092280/html](http://www.nap.edu/books/0309092280/html). 2004.

*The ADAP Watch.* National Alliance of State and Territorial AIDS Directors. April, 2004

*The Journal of Timely and Appropriate Care of People with HIV Disease* 1(1). January 2004.

## Resources

To learn more about ADAP and ways to get involved in advocacy:

AIDS Treatment Data Network  
[www.atdn.org/access/states](http://www.atdn.org/access/states)

Kaiser Family Foundation  
[www.kff.org](http://www.kff.org)

Medical Advocates for Social Justice  
[www.medadvocates.org](http://www.medadvocates.org)

National Association of State and Territorial AIDS Directors  
[www.nastad.org](http://www.nastad.org)

Project Inform  
[www.projectinform.org](http://www.projectinform.org)

San Francisco AIDS Foundation  
[www.sfaf.org/policy](http://www.sfaf.org/policy)

SAVE ADAP (a committee of the AIDS Treatment Activists Coalition)  
[www.atac-usa.org/adap](http://www.atac-usa.org/adap)

Title II Community AIDS National Network  
[www.tiicann.org](http://www.tiicann.org)

Treatment Access Expansion Project  
[www.taepusa.org](http://www.taepusa.org)



The Pangaea Global AIDS

Foundation is dedicated to battling

the impact of HIV at the interna-

tional level, particularly in develop-

ing nations. Find out more about

Pangaea at [www.pgaf.org](http://www.pgaf.org) or

call **415-581-7000**.

# HIV AND **HORMONES**

Liz Highleyman



**THE TERM “HORMONE”** broadly refers to any type of chemical messenger, but is most often used to denote chemicals produced by the endocrine glands. Hormones play a key role in maintaining homeostasis (a steady state of equilibrium) and regulating many bodily processes—everything from growth and metabolism to sexual function and reproduction. Over- or underproduction of endocrine hormones can contribute to a wide variety of medical conditions. Diseases such as HIV that affect the whole body can interfere with proper endocrine function, and hormones, in turn, can affect HIV disease progression.

## The Endocrine System

While exocrine (e.g., sweat, salivary, digestive) glands secrete chemicals directly to their site of action, endocrine (or ductless) glands release hormones into the bloodstream to be transported throughout the body. The major endocrine glands are the hypothalamus, pituitary, thyroid, parathyroids, adrenal glands, Islets of Langerhans in the pancreas, and the gonads (testes in males and ovaries in females); see illustration below. Other cells (for example, in the gastrointestinal tract and the brain) also secrete chemicals that exert endocrine effects.

releasing hormones that direct the pituitary to increase or decrease production of its own hormones, which in turn stimulate subsidiary glands such as the thyroid, adrenal glands, and gonads. The major hypothalamic hormones are growth hormone-releasing hormone (GHRH), thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), gonadotropin-releasing hormone (GnRH), and prolactin-releasing hormone (PRH).

The pituitary, a pea-sized gland located at the base of the brain, is often called the body's "master gland." The anterior (frontal) lobe of the pituitary produces growth hormone (GH, also called somatotropin),

luteinizing hormone (LH)—which regulate the activity of the testes and ovaries; and prolactin, which stimulates mammary gland development and milk production. The posterior (rear) portion of the pituitary secretes antidiuretic hormone (ADH, or vasopressin), which helps regulate the body's fluid balance, and oxytocin, which triggers uterine contractions during labor and the release of milk.

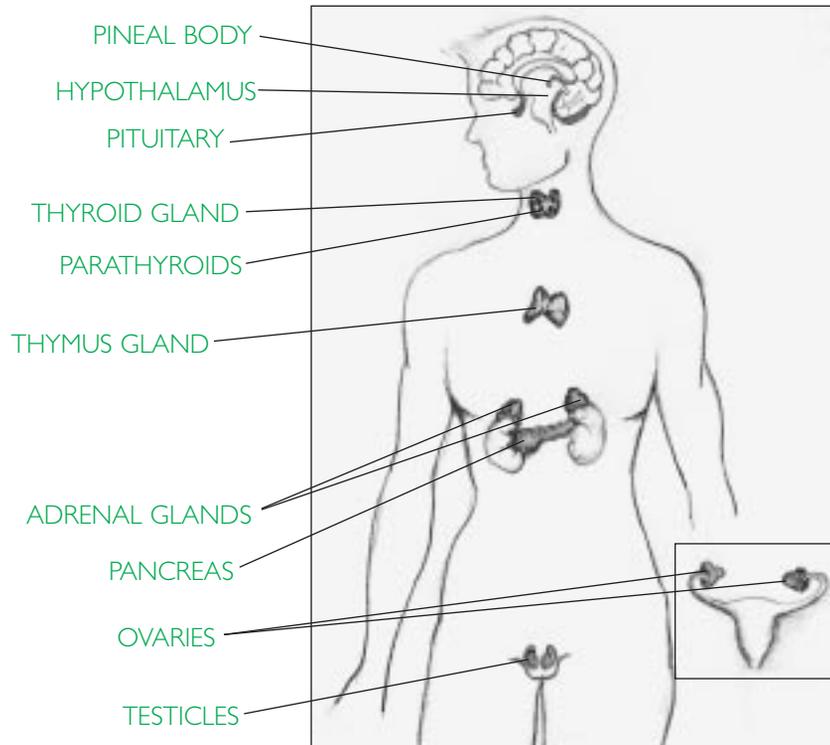
### The Thyroid and Parathyroid Glands

The thyroid, a butterfly-shaped gland located at the base of the neck, produces triiodothyronine (T3) and thyroxine (T4), two hormones that regulate basal metabolic rate. These hormones increase heart rate and blood vessel dilation, affect mood and metabolism, and are necessary for reproduction; they also play an important role in growth and development in children. Overproduction of thyroid hormones (hyperthyroidism) causes rapid metabolism, insomnia, anxiety, weight loss, and heat intolerance. Conversely, underproduction (hypothyroidism) is characterized by slow metabolism, fatigue, depression, weight gain, muscle and nerve dysfunction, and cold intolerance. The thyroid also secretes calcitonin, which helps regulate the body's calcium and phosphorus balance.

Located near the thyroid are four small parathyroid glands, which secrete parathyroid hormone (PTH). Along with calcitonin, PTH helps regulate levels of calcium, which is required for proper neural transmission and muscle function. PTH increases the concentration of calcium in the blood by promoting the release of calcium from bones, decreasing calcium excretion by the kidneys, and enhancing calcium absorption in the intestines. Calcitonin, in contrast, inhibits the release of calcium from bones and increases its excretion in the urine.

### The Adrenal Glands

The two adrenal glands sit on top of each kidney. These glands are comprised of two parts, the medulla (inner part) and the cortex (outer part). The adrenal medulla produces



### The Hypothalamus and Pituitary

The hypothalamus, located in the lower middle part of the brain, is the primary link between the endocrine system and the nervous system. The hypothalamus relays information about the body's external and internal environment from the brain to other glands. The hypothalamus secretes

which promotes normal growth and development (especially in children) and regulates metabolism; thyroid-stimulating hormone (TSH, or thyrotropin), which controls the activity of the thyroid gland; adrenocorticotropic hormone (ACTH, or corticotropin), which stimulates the adrenal cortex; two gonadotropins—follicle-stimulating hormone (FSH) and

# Endocrine Hormones

## HYPOTHALAMUS:

**CRH**—corticotropin-releasing hormone

**GHRH**—growth hormone-releasing hormone

**GnRH**—gonadotropin-releasing hormone

**PRH**—prolactin-releasing hormone

**TRH**—thyrotropin-releasing hormone

## PITUITARY:

### ANTERIOR

**ACTH**—adrenocorticotropic hormone (corticotropin)

**FSH**—follicle-stimulating hormone (gonadotropin)

**GH**—growth hormone (somatotropin)

**LH**—luteinizing hormone (gonadotropin)

### Prolactin

**TSH**—thyroid-stimulating hormone (thyrotropin)

### POSTERIOR

**ADH**—antidiuretic hormone (vasopressin)

### Oxytocin

## THYROID:

### Calcitonin

**T3**—triiodothyronine

**T4**—thyroxine

## PARATHYROID GLANDS:

**PTH**—parathyroid hormone

## ADRENAL GLANDS:

### CORTEX

**Androgens**—e.g., dehydroepiandrosterone sulfate (DHEA-S)

**Glucocorticoids**—e.g., cortisol

**Mineralocorticoids**—e.g., aldosterone

### MEDULLA

**Epinephrine**—adrenaline

**Norepinephrine**—noradrenaline

## ISLETS OF LANGERHANS:

**Glucagon**

**Insulin**

**Somatostatin**

## GONADS (SEX GLANDS):

### OVARIES (female)

**Estrogens**—estradiol, estrone, estriol

**Progesterone**

**Testosterone**

### TESTES (male)

**Testosterone**

two complementary hormones, epinephrine (adrenaline) and norepinephrine (noradrenaline). In response to physiological or psychological stress, the medulla releases epinephrine, which prepares the body for the “fight or flight” response by increasing heart and breathing rate, enhancing muscle contraction, and stimulating the release of fatty acids and glucose (sugar) for energy. In general, norepinephrine has the opposite effects.

The adrenal cortex produces three types of hormones: mineralocorticoids,

glucocorticoids, and androgens. Mineralocorticoids such as aldosterone help regulate the body’s fluid and electrolyte balance. Glucocorticoids such as cortisol are often called the body’s “stress hormones.” Cortisol depresses the immune system and influences glucose and lipid (fat) metabolism, promoting the delivery of glucose to cells to supply energy. Finally, the adrenal cortex produces androgens in both men and women (see the “Sex Glands” section, below).

## The Endocrine Pancreas

The pancreas as a whole is an exocrine gland that secretes digestive chemicals directly into the small intestine. But patches of tissue within the pancreas called the Islets of Langerhans produce endocrine hormones that regulate the metabolism of glucose and lipids. After a meal, islet beta cells secrete insulin, which enables cells to take up glucose and causes the liver and other tissues to store sugar, thus lowering the blood glucose level. Alpha cells secrete glucagon, which has the opposite effect, causing the release of stored sugar and an increase in blood glucose. Other endocrine cells produce somatostatin, which limits the release of GH and inhibits the secretion of insulin and glucagon. (See “Insulin Resistance and Diabetes,” *BETA*, Winter 2004.)

## The Sex Glands

Both men and women produce “male” hormones (androgens) and “female” hormones (estrogens). All steroid hormones, derived from cholesterol, are synthesized through a complex pathway that ultimately leads to estrogen. Androgens (from either the gonads or the adrenal cortex) may be converted to estrogens by an enzyme called aromatase

The testes, or male gonads, are located in the scrotum. When stimulated by LH from the pituitary, the testes produce androgens including testosterone. Testosterone has two types of effects on the body: anabolic effects, which promote muscle building; and androgenic effects, which promote the development of the male sex organs, expression of male secondary sexual characteristics, and normal libido (sex drive). The gonadotropins LH and FSH also control sperm production in the testes.

The ovaries, or female gonads, are located in the pelvic cavity. These glands secrete estrogens and progesterone, as well as a small amount of testosterone. Estrogens promote the expression of female secondary sexual characteristics such as breast development. The ovaries are also the sites of

## Drugs that Can Affect Hormone Levels

### **Carbamazepine (Tegretol)**

Increases metabolism and clearance of cortisol

### **Interferon-alpha, pegylated interferon (Pegasys, Peg-Intron)**

Can cause autoimmune thyroid disease, leading to either hyper- or hypothyroidism

### **Ketoconazole (Nizoral)**

Inhibits synthesis of adrenal corticosteroids; inhibits production of sex hormones by the gonads

### **Marijuana (cannabis)**

May decrease testosterone level; may increase estrogen level

### **Megestrol acetate (Megace)**

Decreases testosterone production; decreases cortisol production; may cause adrenal insufficiency if abruptly discontinued; may cause hyperglycemia

### **Opiates (including heroin, methadone)**

Decrease adrenal gland response to ACTH stimulation; decrease pituitary production of gonadotropins (LH, FSH); increase prolactin production

### **Pentamidine**

Toxic to beta cells of the pancreas; may cause hypoglycemia followed by hyperglycemia and type 2 diabetes

### **Phenytoin (Dilantin)**

Increases metabolism and clearance of cortisol

### **Rifampin (Rifadin, others)**

Increases metabolism and clearance of cortisol

ovum (egg) maturation. A complex interplay of hormones regulates the menstrual cycle and allows for pregnancy. FSH from the pituitary promotes the maturation of an ovum in an ovarian follicle and the secretion of estrogen, which causes cells lining the uterus to proliferate. The rise in estrogen triggers the secretion of LH, which causes the follicle to burst and release the mature ovum, a process known as ovulation. The remains of the burst follicle form a structure called the corpus luteum, which

secretes progesterone. If fertilization occurs, the placenta continues to produce progesterone throughout pregnancy. If not, the progesterone level drops, menstruation occurs, and the cycle begins anew.

## How Do Hormones Work?

Most endocrine activity is governed by a series of feedback loops involving the hypothalamus and the pituitary. When receptors in the hypothalamus sense a decreased level of a specific hormone in the blood, the gland secretes a releasing hormone that tells the pituitary to signal the appropriate subsidiary gland to ramp up its activity. Conversely, as blood levels of a hormone increase, the hypothalamus decreases production of the releasing hormone, in effect “turning off” the subsidiary gland.

For example, when the body is under physical or emotional stress, the hypothalamus relays this information by releasing CRH into a bed of capillaries that feeds the pituitary. CRH causes the anterior pituitary to increase its production of ACTH, which in turn stimulates the adrenal cortex to produce more of the stress hormone cortisol. As cortisol levels rise, the hypothalamus senses this change and stops producing CRH. Without CRH, the pituitary stops secreting ACTH, and the lack of ACTH, in turn, shuts down production of cortisol by the adrenal glands. This negative feedback loop is called the hypothalamic-pituitary-adrenal axis. Similar regulatory pathways exist for the thyroid and the gonads.

Endocrine function can go awry in several ways. The hypothalamus and/or pituitary can produce too much or too little of the hormones that stimulate the activity of other glands. Subsidiary glands may also produce too much or too little hormone, a condition known as primary gland failure. In addition, cell receptors may fail to respond appropriately to a hormone.

## Hormones and HIV/AIDS

Because hormones are involved in so many different bodily processes, it is no surprise that a systemic disease like HIV can affect endocrine function, and vice versa. The first wave of research on endocrine dysfunction in people with HIV occurred in the late 1980s and early 1990s, before the advent of highly active anti-retroviral therapy (HAART). Autopsy studies of people who died from AIDS-related conditions often revealed direct infection of endocrine glands by opportunistic pathogens such as cytomegalovirus (CMV), *Pneumocystis carinii*, or *Mycobacterium avium*. In addition, several drugs used to treat opportunistic illnesses (OIs) can contribute to endocrine dysfunction (see sidebar on this page). Today, it is clear that serious endocrine dysfunction occurs more often in people with AIDS or symptomatic HIV disease than in those with early-stage disease and mild immune suppression.

Some endocrine disorders are associated with serious illness in general. For example, many severe systemic illnesses, including AIDS, are associated with reduced thyroid hormone production, a condition known as euthyroid sick syndrome (meaning the thyroid gland itself is normal, but its function is impaired). In various studies, decreased T3 has been associated with lower CD4 cell counts, active OIs, and severe weight loss.

The endocrine, nervous, and immune systems are interrelated in complex ways that are not yet fully understood. The neuroimmune-endocrine connection is most evident in the hypothalamic-pituitary-adrenal axis, which regulates cortisol production in response to bodily stresses such as infection, inflammation, pain, fear, or emotional distress. Cortisol suppresses many aspects of the immune response, including the proliferation of lymphocytes; the activity of natural killer cells, macrophages, and neutrophils; and the production

## Growth Hormone, Wasting, and Lipodystrophy

of certain cytokines. High cortisol levels are seen in individuals with many types of severe acute or chronic illness, and AIDS is no exception.

Not long after HAART came into widespread use, physicians began noticing similarities between certain metabolic manifestations associated with antiretroviral therapy—such as abdominal obesity and dorsocervical fat pad (“buffalo hump”)—and an uncommon form of excessive cortisol production known as Cushing’s syndrome. But researchers determined that most individuals with asymptomatic HIV disease did not have inappropriately high cortisol levels. Indeed, by slowing disease progression, HAART likely restrains the release of cortisol. Nevertheless, some researchers believe cortisol may play an as yet unknown role in lipodystrophy syndrome (metabolic and body fat disturbances).

It can be challenging to diagnose endocrine problems in people with HIV because certain symptoms may be associated with altered levels of more than one hormone. For example, fatigue and depression may be due to low levels of thyroid hormone, cortisol, growth hormone, or testosterone. In addition, multiple endocrine mechanisms may interact in complex syndromes such as wasting, lipodystrophy, and other metabolic abnormalities.

While severe endocrine problems are seen less often since HAART became widely available, some experts believe that subtle endocrine disorders are still common in people with HIV. Such subtle imbalances may have a major impact on quality of life, and many people with HIV may benefit from testing of hormone levels and supplementation, if appropriate.

### Sex Hormones

In the HAART era, sex hormone imbalances may be the most common endocrine disorders in HIV positive people. Hypogonadism—low testosterone in men and decreased levels of estrogen, progesterone, and/or testosterone in women—can lead to

While growth hormone (GH) promotes growth and development in children, it helps regulate metabolism and body composition in adults. GH deficiency is characterized by loss of muscle mass, increased fat (especially in the abdomen), fatigue, and depression. GH acts through a cytokine called insulin growth factor 1 (IGF-1), produced by the liver, that promotes muscle building and the breakdown of fat. HIV positive people with wasting (as well as HIV negative people suffering from malnutrition) may have GH resistance, a condition in which tissues do not respond normally to the hormone. In contrast to the normal GH/low IGF-1 profile typically seen in individuals with wasting, lipodystrophy appears to be associated with decreased GH secretion.

Recombinant (genetically engineered) human growth hormone has been shown to improve HIV-related wasting. In a controlled study of 178 mostly male HIV positive subjects by Morris Schambelan, MD, of San Francisco General Hospital and colleagues (reported in the December 1, 1996 issue of the *Annals of Internal Medicine*), those taking GH (0.1 mg/kg of body weight) experienced sustained weight gain, increased lean body mass, decreased body fat, and improved exercise performance. GH has also been studied as a therapy for lipodystrophy. In the STARS trial, Donald Kotler, MD, of St. Luke’s-Roosevelt Hospital Center and colleagues found that 4 mg of GH daily or every other day for 36 weeks reduced visceral fat in 142 HIV positive subjects with abdominal fat accumulation. More recently, Kotler reported at the 11<sup>th</sup> Conference on Retroviruses and Opportunistic Infections this past February that low maintenance doses of GH (1–2 mg daily) can sustain normalized body fat distribution after higher-dose GH induction therapy.

There are several brands of recombinant GH, but only Serono Laboratories’ Serostim is approved for HIV-related wasting. Side effects of GH may include muscle and bone pain, carpal tunnel syndrome, edema (swelling), and reduced insulin sensitivity. While GH remains an option for HIV positive people with wasting or lipodystrophy, many physicians prefer to first try other therapies such as testosterone. “Given the high cost and reported side effects of growth hormone therapy... it is best reserved for patients with severe weight loss in whom other therapies are ineffective,” wrote Colleen Corcoran, NP, and Steven Grinspoon, MD, in a review article in the June 3, 1999 issue of the *New England Journal of Medicine*. (For more information on GH, see “The Many Faces of Human Growth Hormone,” *BETA*, Winter 2003.)

a variety of symptoms including fatigue, anemia, depression, loss of libido, impaired sexual function, and decreased fertility. In women, altered sex hormone levels can cause disturbances in the menstrual cycle. Sex hormones also affect body composition, including the synthesis of muscle tissue and the relative distribution of muscle and fat. Both testosterone

and estrogen protect the bones, and the risk of bone loss (osteopenia or osteoporosis) rises as levels of these hormones decrease with age. As people with HIV live longer due to effective antiretroviral therapy, they are subject to the same age-related conditions—including naturally declining sex hormone levels—as their HIV negative counterparts.



## Hypogonadism in HIV Positive Men

Severe hypogonadism is seen most often in men with advanced HIV disease. For example, in an early study of HIV-associated endocrine problems, Adrian Dobs, MD, of Johns Hopkins University in Baltimore and colleagues reported in the March 1988 issue of the *Annals of Internal Medicine* that 6% of asymptomatic HIV positive men, about 40% of men with symptomatic HIV disease, and 50% of men with AIDS were hypogonadal; lower testosterone levels were correlated with weight loss and lower CD4 cell counts. Likewise, Steven Grinspoon, MD, and colleagues from Massachusetts General Hospital (MGH) reported in the November 1996 issue of the *Journal of Clinical Endocrinology and Metabolism (JCEM)* that in a study of 75 men with AIDS wasting, about one-half had free (bioavailable) testosterone levels below the normal range for men their age.

In contrast, Julio Collazos, MD, of Hospital de Galdakao in Vizcaya and colleagues reported in the April 12, 2002 issue of *AIDS* that in a study of nearly 200 clinically stable HIV positive men (average CD4 cell count 451 cells/mm<sup>3</sup>; 64% with undetectable viral load), most subjects had testosterone levels within the normal range. Men receiving no anti-HIV therapy had the lowest testosterone, while those using a regimen combining three classes of antiretroviral drugs had the highest levels. Among the 15 men who had both pre- and post-treatment testosterone measurements, levels increased after starting HAART. But because testosterone levels normally begin to decline around age 40 (a phenomenon known as “andropause”), the beneficial effects of HAART on hypogonadism may be offset as treatment enables HIV positive men to live to older ages.

Altered testosterone levels have been linked to wasting and other

changes in body composition, but the cause and effect relationship is unclear. Severe weight loss can lead to decreased production of the gonadotropins that direct the production of testosterone; in turn, low testosterone, which stimulates the buildup of muscle, contributes to wasting. (Wasting and body composition changes are also associated with growth hormone abnormalities; see sidebar on page 38.)

Other symptoms associated with low testosterone include fatigue, depression, loss of libido, and impaired sexual function (e.g., erectile dysfunction, or impotence). For example, in the January 2000 issue of *JCEM*, Grinspoon and colleagues reported that in a study of 52 hypogonadal and ten eugonadal (normal testosterone level) men with HIV-related wasting, those with lower testosterone levels had higher scores on the Beck Depression Inventory (that is, they were more depressed).

To help diagnose hypogonadism, researchers from St. Louis University devised a questionnaire called Androgen Deficiency in Aging Men, or ADAM; though it was developed to assess normal decreases in androgen levels as men age, the symptoms of testosterone deficiency are the same regardless of cause (see sidebar on page 40).

## Androgen Supplementation in Men

Diagnosing hypogonadism can be difficult because normal levels vary greatly from person to person. To get a complete picture, different forms of testosterone may be measured. Normally, most testosterone is bound to carrier proteins in the blood; only about 2% is unbound. A total testosterone test measures both bound and unbound hormone. A free testosterone test measures only unbound, or bioavailable, testosterone. A typical normal range for total testosterone is 250–1,200 nanograms/deciliter (ng/dL), while a normal free testosterone range is about 100–200 ng/dL. Total testosterone levels of 250–400

ng/dL are considered borderline low, and may have functional consequences. However, testosterone levels depend on age; older men have lower normal levels than younger men.

When diagnosing endocrine problems it is important to look not just at absolute levels of specific hormones, but also at the balance between them. For example, if a man begins to convert more testosterone to estrogen, his androgen/estrogen ratio will shift and he may begin to experience “feminizing” symptoms such as breast growth, even if his testosterone remains within the statistically normal range. Also, a testosterone level within the normal range may be inadequate for a given individual if his usual level is higher. Some experts recommend getting a baseline testosterone measurement soon after HIV is diagnosed, against which later measurements may be compared.

Hypogonadal men can be treated with supplemental testosterone or synthetic androgens. Testosterone may be administered in several forms. Testosterone cypionate or enanthate are injected intramuscularly, usually every 2–4 weeks. While this is the least expensive method, cyclical injections provide fluctuating blood levels of the hormone, peaking soon after administration and decreasing over time. Transdermal testosterone patches provide a more steady level. The Testoderm patch is applied daily to the scrotum, while the newer Androderm patch is applied daily to the back, abdomen, upper arm, or thigh. Testosterone gel (AndroGel) and creams are also available. Oral testosterone pills are not commonly used since they can cause liver toxicity.

Injected testosterone may increase overall body weight and especially lean body mass. In the July 1, 1998 issue of the *Annals of Internal Medicine*, Grinspoon and colleagues reported that hypogonadal men with HIV-associated wasting gained muscle mass and reported improved appearance and quality of life after six months of testosterone therapy (one

## St. Louis University Androgen Deficiency in Aging Men (ADAM) Screening Questionnaire

injection every three weeks).

Grinspoon's team also found that Beck Depression Inventory scores decreased (indicating improvement) in men treated with testosterone. Judith Rabkin, PhD, MPH, and colleagues from the New York State Psychiatric Institute reported in the February 2000 issue of the *Archives of General Psychiatry* that 74% of HIV positive men receiving biweekly testosterone injections reported increased libido, 59% had improved energy levels, and 58% of men with depression reported improved mood.

Testosterone skin patches are also effective. Shalender Bhasin, MD, of the University of California at Los Angeles and colleagues reported in the September 1998 issue of *JCEM* that men using Androderm patches experienced greater increases in lean body mass, larger decreases in fat, and more improvement in quality of life compared with men using placebo patches.

More recently, testosterone has been studied as a treatment for lipodystrophy and other metabolic manifestations associated with HAART. In individuals with mixed lipodystrophy (loss of fat from the limbs and face accompanied by abdominal fat gain), the hormone may both decrease fat and increase lean tissue mass. In the January 2000 issue of *JCEM*, Colleen Hadigan, MD, and colleagues (part of the MGH team) reported that in a study of 52 HIV positive hypogonadal men with wasting, those who received supplemental testosterone experienced improved insulin sensitivity as their lean body mass increased. Further, Wesley Fairfield, MD, from MGH and colleagues reported that testosterone therapy led to increased bone density in eugonadal HIV positive men with osteopenia.

In addition to testosterone, synthetic androgenic steroids may also be used. Some have a more androgenic (masculinizing) effect, while others have a more anabolic (muscle-building) effect. The latter may provide some of the benefits of testosterone

- Do you have a decrease in libido (sex drive)?
- Do you have a lack of energy?
- Do you have a decrease in strength and/or endurance?
- Have you lost height?
- Have you noticed a decreased "enjoyment of life"?
- Are you sad and/or grumpy?
- Are your erections less strong?
- Have you noticed a recent deterioration in your ability to play sports?
- Are you falling asleep after dinner?
- Has there been a recent deterioration in your work performance?

without unwanted virilization, which is especially important for women, as discussed below. Steroids with more anabolic effects include nandrolone decanoate (Deca-Durabolin), which is injected every 1–2 weeks, and oxandrolone (Oxandrin), which is taken orally every day. Julian Gold, MD, and colleagues from Prince of Wales Hospital in Sydney reported in the June 1996 issue of *AIDS* that nandrolone increased lean body mass, enhanced exercise performance, and improved quality of life in HIV-infected hypogonadal men. Oxandrolone, too, has been shown to improve wasting in HIV positive men, and the drug is FDA-approved for this indication. For example, Joseph Berger, MD, and colleagues reported in the December 1996 issue of the same journal that daily treatment with either 5 mg or 15 mg of oxandrolone had a positive impact on the weight and well-being of men with HIV.

The potential side effects of testosterone and its synthetic analogs include acne, elevated liver enzymes, altered blood lipids (especially decreased HDL, or "good" cholesterol), mood changes, painful erections, gynecomastia (breast enlargement in men), sleep apnea, edema, excess red blood cell production, high blood pressure, and virilizing effects such as male pattern baldness. In addition, supplemental androgens influence the hypothalamic-

pituitary-gonadal axis and shut down natural production of testosterone, which can lead to testicular atrophy (shrinkage). Side effects are less likely when using physiological doses to approximate natural levels, as opposed to supraphysiological doses that exceed the normal range (e.g., for bodybuilding). When using patches, gels, or creams, which deliver a steady dose of testosterone, blood levels should be measured soon after supplementation begins and regularly (every 6–12 months) during the course of therapy.

The long-term effects of androgen therapy in HIV positive men are unknown. Because androgens can lower the level of cardioprotective HDL cholesterol, there is concern that they may increase the risk of heart disease, especially when combined with antiretroviral drugs that also cause dyslipidemia (altered blood fats). But in the September 1, 2003 *Clinical Infectious Diseases* supplement, Bhasin suggested that by reducing visceral fat and improving glucose metabolism, androgen therapy may actually decrease the risk of cardiovascular disease in HAART-treated men. Increased cancer risk is another concern, and men taking supplemental androgens should receive regular prostate cancer screening.

Grinspoon recommends that all men with HIV-related wasting should

be screened for testosterone deficiency and given supplements if their levels are low. Douglas Dieterich, MD, of Mt. Sinai School of Medicine in New York City suggests that men with symptoms of hypogonadism should be tested and treated even if they have not experienced severe weight loss.

While testosterone replacement therapy is beneficial for HIV positive men with hypogonadism, it is unclear whether extra testosterone offers additional benefit for men who already have normal levels. While some studies have shown that supplemental androgens can increase lean body mass, reduce fat, and improve well-being even in eugonadal men, such use remains controversial since the long-term effects of supraphysiological testosterone are unknown.

## WOMEN

### Sex Hormones in HIV Positive Women

Since the beginning of the epidemic, women with HIV have reported missed periods, unusually light or heavy periods, severe premenstrual syndrome (PMS), and early menopause. These can be caused by altered sex hormone levels, but other factors—such as opiate use, certain psychiatric medications, or stress—may also be responsible for such changes. (For a discussion of fertility in women with HIV, see page 45.)

Despite the frequency of anecdotal reports, controlled studies of menstrual irregularities in HIV positive women have yielded inconsistent results. Some research suggests that HIV has little or no impact on menstrual function. Based on interviews with 197 HIV positive and 189 HIV negative women, Tedd Ellerbrock, MD, of the Centers for Disease Control and Prevention (CDC) and colleagues reported in the June 1996 issue of *Obstetrics and Gynecology* that the number and duration of menstrual cycles did not differ significantly

between the two groups. In the March 1994 issue of the same journal, P. Shah and colleagues reported no significant differences in rates of amenorrhea (lack of periods), sparse or heavy menstruation, or menstrual cramps between HIV positive and HIV negative women. In addition, no association was seen between CD4 cell count and menstrual irregularities, nor were there differences between symptomatic and asymptomatic HIV positive women. In another study Susan Cu-Uvin, MD, of Brown University and colleagues found no significant differences in progesterone and estradiol (a form of estrogen) levels based on CD4 cell count, baseline viral load, or type of antiretroviral therapy.

In contrast, Keith Chirgwin, MD, of the State University of New York Health Science Center and colleagues reported in the August 1996 issue of the *Journal of AIDS (JAIDS)* that HIV positive women without AIDS were more likely than HIV negative women to go longer than six weeks between periods and were more likely to have amenorrhea for more than three months. And based on a large study of 802 HIV positive and 273 HIV negative women, Sioban Harlow, PhD, of the University of Michigan in Ann Arbor and colleagues reported in the May 2000 issue of *JAIDS* that women with HIV were slightly more likely to have unusually short (less than 18 days) or very long (more than 90 days) menstrual cycles, and that higher viral load and lower CD4 cell count were associated with increased cycle variability and unusually frequent periods.

According to Kathleen Squires, MD, of the University of Southern California in Los Angeles, menstrual irregularities, intensified premenstrual symptoms, and early menopause likely have more to do with advanced illness and wasting than with HIV per se. (Among HIV negative women, it is well known that young women with anorexia nervosa and women athletes with low body fat percentages may stop menstruating.) Indeed,

in a study of 43 HIV positive women with a range of CD4 cell counts published in the May 1997 issue of *JCEM*, Grinspoon and colleagues found that women with wasting were more likely to have sparse or absent periods compared with those who had stable weight or only mild weight loss; among women with serious wasting, 38% were amenorrheic compared with 17% of women without weight loss. In addition, the euthyroid sick syndrome (described above) is associated with irregular menstruation.

Menstrual problems in HIV positive women are seen less often since the advent of HAART, but anti-HIV treatment itself may sometimes contribute to such irregularities. For example, Henrik Nielsen, MD, of Aalborg Hospital in Denmark reported in the March 6, 1999 issue of *The Lancet* on four cases of hypermenorrhea (unusually heavy periods) in women taking ritonavir (Norvir); hypermenorrhea is a concern because it can lead to anemia due to excessive blood loss.

Much remains to be learned about how female sex hormones and the immune system interact. For example, hormonal factors appear to influence women's vulnerability to HIV infection (see sidebar on page 42). Studies have shown that HIV positive women have higher CD4 cell counts than men who have been infected for a similar length of time, and show greater disease progression than men with the same CD4 cell counts. Hormonal factors may also help explain differences in how women and men metabolize antiretroviral drugs.

### Hormone Replacement Therapy for Women

As HIV positive women live longer, they are subject to the same age-related hormonal changes as their HIV negative counterparts. The use of hormone replacement therapy (HRT) in women with or without HIV is currently controversial. Once routinely recommended both for ameliorating acute menopausal symptoms and for preventing problems such as osteoporosis,

## Sex Hormones and HIV Transmission

Research suggests that female sex hormones play a role in HIV transmission and acquisition. Some studies indicate that levels of HIV in women's genital fluids fluctuate over the course of the menstrual cycle as hormone levels change, which could have implications for sexual and mother-to-child transmission. In addition, Chia Wang, MD, of the University of Washington and colleagues reported in the January 23, 2004 issue of *AIDS* that use of hormonal contraceptives was associated with increased cervical shedding of HIV.

Hormone levels also appear to affect women's vulnerability to infection. In research on female macaque monkeys, administration of estrogen appeared to protect the animals from infection with SIV (a simian virus similar to HIV), while monkeys who received high-dose progesterone were about seven times more susceptible, likely due to thinning of the linings of the vagina and uterus. Other research suggests that the use of oral or injected hormonal contraceptives without additional barrier methods increases the likelihood that women will contract HIV. In the March 5, 2004 issue of *AIDS*, Ludo Lavreys, MD, and colleagues from the University of Washington in Seattle reported that in a study of nearly 1,500 female sex workers in Mombasa, Kenya, women using hormonal contraceptives were at increased risk for HIV infection (1.5 times higher with oral contraceptives; 1.8 times higher with injected Depo-Provera). Looking at a subset of more than 150 women who seroconverted, the same team found that women using hormonal contraceptives at the time of infection were more likely to have a higher viral load set-point and multiple viral variants, which are associated with more rapid disease progression.

heart disease, and cognitive decline, long-term HRT has fallen out of favor in the wake of studies showing that estrogen, with or without progesterone, appears to confer more risks than benefits.

Menopause typically ensues between the late thirties and late fifties. During menopause and the preceding period known as perimenopause, declining estrogen levels can cause symptoms such as hot flashes, night sweats, insomnia, fatigue, depression, irritability, forgetfulness, and vaginal thinning and dryness. The more intense symptoms typically improve over two to three years as hormone fluctuations even out. A careful differential diagnosis is necessary to avoid confusing symptoms of menopause with those related to HIV itself, OIs, or antiretroviral therapy.

For young women who experience premature amenorrhea before the normal age of menopause, oral contraceptives may be used to restore levels of estrogen and progesterone

and re-establish normal menstrual cycles. For older women undergoing menopause, physicians have traditionally offered HRT using either oral estrogen (e.g., Premarin) or estrogen plus progesterone (e.g. Prempro).

In July 2002 the estrogen/progesterone arm of the Women's Health Initiative (WHI) HRT study, which included more than 160,000 postmenopausal women, was discontinued after data showed that combination HRT increased the risk of breast cancer, heart attacks, and strokes (although the absolute risk was small). HRT did lower the risk of hip fractures and colon cancer, but the researchers concluded that the overall risks outweighed the benefits. This past March the estrogen-only arm of the study was also halted after seven-year data revealed that estrogen not only failed to provide the hoped-for cardiovascular benefits, but also appeared to slightly raise the risk of strokes. (Because estrogen without progesterone increases the risk for uterine cancer, this arm included

nearly 11,000 women who had undergone hysterectomies.)

The WHI results were "earth-shaking," according to Lori Kamemoto, MD, of the University of Hawaii in Honolulu. In the wake of the WHI news, Kamemoto's planned ACTG study of HRT in postmenopausal HIV positive women was put on hold. As it stands, the risks and benefits of HRT in women with HIV remain unknown. HIV positive women could conceivably benefit from the bone-preserving effects of estrogen, especially since some studies suggest that HAART or HIV itself are associated with a higher risk of osteoporosis. At the same time, women on HAART may be at higher risk for HRT-related heart attacks or strokes due to dyslipidemia and other side effects associated with antiretroviral therapy, and may be at greater risk for cancer due to immune suppression.

Despite this uncertainty, many physicians believe that HRT remains a viable short-term strategy for relieving disabling menopausal symptoms. "I give the same recommendations to women with HIV as I do to HIV negative women," says Kamemoto. "If you have severe, intractable postmenopausal symptoms, and you've tried waiting it out, perhaps you're one of those who need HRT."

But most experts now agree that routine, long-term use of HRT solely to prevent heart disease or osteoporosis is inappropriate. Medications such as alendronate (Fosamax) and risendronate (Actonel) may help prevent bone loss without the risks of HRT.

For women with low levels of estrogen and/or progesterone, there are other options beside oral hormone supplements. Estrogen and progesterone are also available in creams, patches, and vaginal rings that deliver lower doses and thus may not carry the same risks. Several natural remedies are sometimes recommended as alternatives to HRT, but these generally have not been studied in controlled trials. Soy, which contains

plant-derived estrogens, and black cohosh both appeared to relieve menopausal symptoms in clinical studies. Vitamin E, vitamin B complex, magnesium, and evening primrose oil may help ameliorate symptoms such as hot flashes, cramps, bloating, and mood swings.

### Androgen Therapy for Women

HIV positive women may also experience some of the same problems as their male counterparts: muscle wasting, fat gain, fatigue, depression, loss of libido, and impaired sexual function. And, as in men, these symptoms may be due to low testosterone. Normal testosterone levels vary widely from woman to woman; a typical normal range is 20–100 ng/dL for total testosterone or 1–2 ng/dL for free testosterone.

Low testosterone levels appear to be common in HIV positive women, especially those with wasting syndrome. In Grinspoon's 1997 study of women with HIV, 66% with severe wasting, 50% with early wasting, and 33% with no wasting had free testosterone levels below the normal range for healthy women of the same age. Likewise, in the February 15, 2003 issue of *Clinical Infectious Diseases*, Jeannie Huang, MD, and colleagues from MGH reported that about one-half of HIV positive women in another study had low free testosterone levels, compared with 8% of uninfected women; among the HIV positive women, 58% of those with severe wasting had low free testosterone, compared with 24% of those with less significant weight loss.

Testosterone supplements may be used in women, but require caution to avoid unwanted, and possibly irreversible, virilizing side effects such as excessive facial or body hair growth (hirsutism), hoarseness or deepening of the voice, and clitoral enlargement. For this reason, testosterone patches, creams, or gels are preferred over higher-dose testosterone injections. Compounding pharmacies can prepare creams that contain the desired dose. If virilizing side effects or

menstrual changes occur, doses should be lowered or therapy discontinued. Testosterone is contraindicated in women who are pregnant or trying to become pregnant.

In a study published in the August 1998 issue of *JCEM*, Karen Miller, MD, and colleagues, also part of the MGH research group, reported that in a study of 53 HIV positive women with wasting and low testosterone levels, administration of physiological doses of testosterone (one patch twice weekly) was associated with weight gain and improved quality of life without virilizing side effects. In the April 26, 2004 issue of the *Archives of Internal Medicine*, Sara Dolan, NP, and colleagues from the MGH team reported that twice-weekly testosterone patches improved muscle function in this population. Importantly, however, more testosterone is not necessarily better. In Miller's study, the same benefits were not seen in women who received supraphysiological doses of testosterone (two patches twice weekly).

Some researchers think anabolic steroids with less androgenic effects, such as nandrolone and oxandrolone, may be a better option for women, although these agents may not provide the same benefits in terms of improving libido or relieving depression. At the 8<sup>th</sup> Retrovirus conference in February 2001, Kathleen Mulligan, MD, from San Francisco General Hospital presented results of a study of 38 HIV positive women with wasting randomly assigned to receive nandrolone or placebo. The women in the nandrolone arm experienced increased total weight and lean body mass, while virilizing side effects were rare. To date, however, neither nandrolone nor oxandrolone has been adequately studied in women with HIV. Grinspoon recommends only natural testosterone, since synthetic anabolic steroids may adversely affect the liver. Another option is combined testosterone/estrogen therapy (e.g., Estratest). For some women, supplementing both androgens and estrogens

appears to improve menopausal symptoms, energy, and libido more than either alone.

## Conclusion

Even in the HAART era, endocrine disorders and hormone imbalances are common in men and women with HIV. Several symptoms frequently seen in HIV positive individuals—such as wasting, metabolic abnormalities, fatigue, and depression—may be associated with multiple endocrine abnormalities.

Much remains to be learned about the use of hormone therapy in people with HIV, especially in conjunction with HAART. "Using testosterone or anabolics may help with the body habitus changes in lipodystrophy, but it may exacerbate the lipid disorders. Using growth hormone may also counteract the body changes, but it may exacerbate the insulin resistance seen in these patients," Dieterich wrote in a commentary in the December 9, 1998 issue of the *Journal of the American Medical Association*. "What is the answer?"

The answer awaits further research, including more studies of how the endocrine and immune systems interact in the context of HIV disease.

In the meantime, people with HIV who have symptoms of hormonal problems should seek a provider or medical team that has experience treating both HIV and endocrine disorders. If hormone supplements are used, levels should be checked soon after therapy is started and regularly thereafter. Other tests, including liver enzymes and blood lipids, also should be performed regularly to monitor potential side effects of hormone therapy.

People with HIV and their providers should be alert to the possibility of interactions between hormones and antiretroviral drugs. It has been demonstrated that several protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) interact with the ethinyl

## Hormones and Transgender Individuals with HIV

estradiol and/or norethindrone in oral contraceptives, either raising or lowering blood levels. However, it is not yet clear how antiretroviral drugs interact with other types of hormone therapy, or how they affect natural hormone levels. Because drug interactions primarily occur in the liver when oral medications are used, administering hormones in the form of patches, creams, or gels may alleviate this concern.

As Squires notes, in the era of HAART, people with HIV and their clinicians now must think about the general health conditions associated with aging in addition to HIV-specific concerns. Although declining hormone levels are part of the natural aging process, supplementation can play an important role in improving functional capacity and quality of life for individuals experiencing clinical symptoms associated with hormone deficiencies.

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HIV positive transgender individuals who are using hormone therapy for gender transition face some special concerns. Individuals transitioning from male to female usually take oral estrogen (with or without androgen-blocking drugs), while individuals transitioning from female to male typically use injected testosterone and sometimes aromatase inhibitors to block the conversion of testosterone to estrogen.

Hormone doses used for sex reassignment are higher than those used for contraception or hormone replacement therapy. The risk of adverse short-term side effects and long-term consequences (such as liver problems, cancer, and heart disease) is therefore greater. The effects of large hormone doses on HIV positive transgender individuals have not been well studied, nor has the interaction between hormones and antiretroviral medications.

Concurrent use of hormone therapy, especially oral estrogens, and certain NNRTIs and PIs may lead to either increased or decreased hormone levels. This has been seen with the ethinyl estradiol and norethindrone in oral contraceptives. If drug interactions lead to lower blood estrogen levels, this may cause the return of male features such as facial and body hair growth. Levels of anti-HIV medications could potentially also be affected, leading to either subtherapeutic antiretroviral drug levels or intensified side effects. Transgender men usually take large testosterone doses by injection, thus bypassing the drug-metabolizing cytochrome P450 enzyme system in the liver. Interactions have not been documented between antiretroviral drugs and testosterone, although the possibility cannot be excluded.

Transgender individuals with HIV who are taking hormones should receive care from a physician or medical team that has experience with both HIV treatment and hormone therapy for sex reassignment. While taking hormones, it is important to have levels checked regularly, along with monitoring tests for side effects such as liver toxicity and abnormal blood fat levels.

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# Fertility, Conception,

The subject of HIV/AIDS as it relates to fertility and conception has begun to generate interest among biological and sociobehavioral researchers. As a result, a better understanding of the fertility-related intentions and desires of HIV positive individuals, as well as advancing knowledge regarding reproductive technologies, now offer the hope of parenthood to childless couples.

Shari Margolese



# and HIV

## A Desire for Children

Significant numbers of people with HIV intend to have children. “Fertility Desires and Intentions of HIV Positive Men and Women,” a study published in 2001 in *Family Planning Perspectives*, concluded that 29% of HIV positive women and 28% of HIV positive heterosexual or bisexual men who received medical care in the U.S. desired children in the future. Yet while many women and men with HIV desire children, fertility and conception issues may complicate the realization of this dream. Indeed, of those desiring children among the total sample of 1,421 subjects aged 20–44 mentioned above, 31% of women and 41% of men did not expect to have any.

## Fertility

One effect of HIV/AIDS on individual women and society at large is a change in fertility levels, which is influenced in part through altered behavior. In studies done in sub-Saharan Africa, behaviors that have been largely influenced by AIDS education, such as increased condom use, delayed onset of sexual relations, older age at first union, and fewer premarital sexual relations, have driven down fertility rates. Within the same population, lower rates of remarriage after an AIDS-related death of a partner due to stigma associated with the surviving partner may also diminish fertility levels.

Behavioral influences may also lead to higher fertility rates. The number of sub-Saharan African couples who reconcile following marital infidelity has increased; these couples tend to go on to have more children. In societies with high HIV/AIDS rates, some couples may desire larger

families to ensure survival of children, though others limit family size due to concerns about leaving orphans behind after an early death. In countries where HIV/AIDS treatment is widely available, positive parenting is on the rise. The risk of mother-to-child transmission is as low as 2% in these areas, and treatment has prolonged life expectancy for many potential parents with HIV.

Biological mechanisms also influence fertility rates in HIV positive women and men. Research has shown that women with HIV may find it more difficult to conceive than their HIV negative counterparts. HIV infected women experience reduced pregnancy rates and higher rates of both planned abortion and miscarriage. HIV/AIDS may induce sterility, increase fetal mortality, decrease production of spermatozoa, and sometimes decrease frequency of sexual intercourse, all contributing to declining fertility.

A look at three studies in HIV positive women shows some of the effects of HIV infection on pregnancy.

Amanda Ross of the Swiss Tropical Institute in Basel and colleagues studied a cohort of 191 women (92 HIV positive and 99 HIV negative at enrollment), aged 15–49, in southwest Uganda between 1990 and 2001 to better understand the association between HIV disease progression and the incidence of pregnancy. Among the women with HIV, sexual intercourse became less frequent as HIV disease progressed. In their analysis, Ross’ team found that “fertility is reduced from the earliest asymptomatic stage of HIV infection resulting from both a reduced incidence of recognized pregnancy and increased fetal loss. The greatest reduction in fertility was observed following progression to AIDS when there was a very low incidence of recognized pregnancies.” (A recognized pregnancy refers to the implantation and survival of an embryo in the lining of the

uterus.) These data were published in the March 26, 2004 issue of *AIDS*.

An earlier study of 412 HIV positive women in Paris and southeastern France from 1988 to 1993 by Isabelle De Vincenzi of Saint-Maurice National Hospital and colleagues found that the incidence of pregnancy decreased by more than half, from 20.4 per 100 person-years before HIV diagnosis to 7.9 per 100 person-years after HIV diagnosis. (A person-year a shorthand term used by epidemiologists to make comparisons.) The study also showed that the proportion of pregnancies voluntarily interrupted more than doubled from 29% to 63% after HIV diagnosis. The percentage of miscarriages and ectopic (outside the womb) pregnancies increased significantly from 8.3% to 25.4% of those conceived before and after HIV diagnosis, respectively. Also, the proportion of women who were sexually inactive rose four-fold, from 5% before to 20% after HIV diagnosis. These data were published in the March 11, 1997 issue of *AIDS*.

Carla D'Ubaldo of Lazzaro Spallanzani Hospital in Rome and colleagues studied a cohort of 272 women from 12 Italian cities in the 1990s and found that 63% of the women with HIV had an intentional abortion, compared with a lower proportion (45%) of the HIV negative women. These data were published in the June 18, 1998 edition of *AIDS*.

## The Role of HIV

Little data are available to clarify the specific role of HIV in fertility. Researchers hypothesize that the virus not only plays a direct role in reduced fertility among HIV positive people, but also has an indirect impact for positive women and men.

Directly, HIV infection may influence women to voluntarily terminate a pregnancy out of fear of leaving an orphan or transmitting HIV to the child. D'Ubaldo's team offered possible explanations for increased spontaneous abortion (miscarriage) in HIV positive women. They suggested that HIV affects the placenta by interfering with the transfer of important nutrients to the fetus, or that the virus causes abnormal development of the embryo. Other theories include a direct relationship between HIV and the fetal thymus gland, as well as an increased risk of infection due to the weakened immune system of the mother. HIV may also directly influence the ability of HIV positive men to produce healthy sperm.

Indirectly, women with HIV may experience infertility due to coinfection with another sexually transmitted disease. Complications of HIV, such as increased risk of cervical abnormalities, early menopause, pelvic inflammatory disease (which can cause scarring of the Fallopian tubes), and severe wasting may also contribute to infertility in women.

## Conception

Conception, or becoming pregnant, is of particular concern for serodiscordant couples (those in which only one partner is HIV positive). Safer sex is recommended, which usually prevents pregnancy. However, assisted reproductive technologies may aid serodiscordant couples in achieving pregnancy while at the same time minimizing the risk of HIV transmission to the uninfected partner.

Several European fertility clinics, as well as a few American facilities, have experience in providing both intrauterine (within the uterus) insemination and *in vitro* (test tube) fertilization to serodiscordant couples without seroconversion of uninfected female partners. To reduce the risk of HIV transmission, sperm must be isolated from the semen and "washed." Sperm washing must be done in a laboratory. Unfortunately, it is not possible to remove all viral particles from washed sperm, contributing to the controversial nature of this procedure. Yet studies involving washed sperm show that seroconversion rates are low and that many couples are willing to take the risk to become parents.

"[HIV]-serodiscordant couples are actively seeking reproductive assistance and often consider or practice unsafe measures to achieve pregnancy. Reproductive issues and concerns unique to these couples need to be addressed before [fertility] treatment," concluded Jeffrey Klein, MD, of Columbia-Presbyterian Medical Center in New York City and colleagues in the May 2003 edition of *Obstetrics and Gynecology*. These researchers found that some HIV-serodiscordant couples are willing to go to great lengths, and consequently to great risk or expense, to conceive.

Fifty serodiscordant couples interested in undergoing assisted reproduction to avoid HIV transmission were questioned by Klein and his team concerning their attitudes about starting a family. By design, the men were HIV positive, aged 26–51, and asymptomatic. The women were HIV negative, aged 24–45. Most couples (44 of 50) were married or in long-term relationships. Before study enrollment, nine of the 50 couples had conceived and delivered a child. Previous timed intercourse (unprotected intercourse during peak fertile periods) occurred in 8% of the couples. Six individuals stated that they would risk HIV infection and proceed with timed intercourse if no other alternative existed. Forty-eight percent said they would prefer artificial insemination with donor sperm if assisted reproduction failed or were unavailable. Forty-three percent would pursue posthumous (after the death of one partner) conception if cryopreserved (frozen) sperm or embryos were available in the event of the partner's death. Most couples discussed the possibility of single parenting (90%) or the possibility for adoptive parenting (58%). All couples were aware of HIV transmission risk to the female partner, and 92% understood that their child might contract HIV.

Jeanine Ohl, MD, of the Centre d'AMP in Strasbourg and colleagues published their observations of assisted reproduction techniques for serodiscordant couples over 18 months in the June 2003 edition of *Human Reproduction*. Ohl's team concluded that assisted reproductive technology, particularly injection of an egg with a single sperm (intracytoplasmic sperm injection, or ICSI), provided HIV positive men with a safe and highly effective means of fathering children. Among 57 serodiscordant couples, 12 of 39 in which the male was infected produced a total of 14 children. Seroconversion was not observed in any partners of HIV positive men. ICSI was the most successful assisted reproductive technique, resulting in pregnancies in 49% of all transferred embryos. *In vitro* fertilization was less successful, and eight attempts at intrauterine insemination (IUI) did not result in any pregnancies. Of the ten HIV positive women treated, only one became pregnant; Ohl attributed this low rate to possible premature ovarian failure (loss of ovarian function in women under 40).

Further evidence of favorable outcomes using assisted reproduction technologies is found in the August 20, 2003 edition of the *American Journal of Perinatology* as reported by Jane Cleary-Goldman, MD, and colleagues from New York Presbyterian Medical Center. In this study, 25 serodiscordant couples underwent *in vitro* fertilization and embryo transfer (IVF-ET) with ICSI. During this procedure, mature eggs are removed from a woman's ovaries and fertilized with washed sperm in a laboratory. The fertilized eggs are then transferred back into the woman's uterus where, it is hoped, a pregnancy will occur. Investigators reviewed outcomes of HIV negative women after IVF-ET with ICSI from January 1, 1997, to June 1, 2002. Twenty-seven pregnancies were successfully conceived, delivering 40 babies (16 singletons, nine sets of twins, and two sets of triplets). The mean (average) gestational age at delivery was 37 weeks, and the mean birth weight was 2,646 g (about 5.8 lbs). Caesarean sections (C-sections) were performed in 70% of births. Preterm delivery (under 37 weeks) occurred in seven pregnancies, and low birth weight (below 2,500 g or about 5.5 lbs) was observed in eight pregnancies. No HIV seroconversions were detected at delivery, and all of the mothers and their offspring remained HIV negative beyond three months postpartum.

## Access

Guidelines for providing infertility treatment to HIV positive people vary across the world. Several countries allow assisted reproductive therapies for HIV positive men, but few allow it for women with HIV. In the February 2002 edition of *Fertility and Sterility*, the Ethics Committee of the American Society for Reproductive Medicine published new guidelines on treating infertility in HIV positive individuals. According to the committee, physicians practicing reproductive medicine should not deny treatment to

anyone with HIV. Ethically as well as legally, providers have the same obligation to treat HIV positive patients as those suffering from any other chronic disease. The committee further recommends that when a clinic lacks the skills and facilities to manage people with HIV, the individuals should be referred to a clinic with adequate resources. The guidelines also outline acceptable procedures for conception, including artificial insemination with the partner's sperm if the female partner is HIV positive; artificial insemination using sperm-washing techniques and testing of the washed sperm for virus if the male partner is HIV positive; and *in vitro* fertilization and ICSI.

HIV positive couples who require the assistance of reproductive technologies to conceive are very limited in their access to care. Until recently, the Special Program of Assisted Reproduction (SPAR), a program of the U.S. Centers for Disease Control and Prevention (CDC), permitted only *in vitro* fertilization using washed sperm. The procedure is expensive, costing about US\$7,000 per ovulation cycle. In 2002 the recommendations were updated to include the *in utero* (in the uterus) method of insemination. A few other countries, such as France and Canada, may offer sperm washing and other technologies on a limited basis to HIV positive or serodiscordant couples.

## Conclusion

HIV positive couples are not limited to conventional childbearing methods. Other avenues to parenthood include adoption and sperm donation from a known donor or sperm bank. While stigma continues to be a barrier for couples seeking to become parents by these means, many have been successful. For those seeking unconventional methods of parenting, such as surrogacy (when another woman carries the child), little information is available specific to HIV positive couples. However, it is likely that similar rules would apply regarding implantation of potentially infected tissue into an HIV negative woman.

As more HIV positive couples consider parenthood, it is likely that fertility services will slowly become more available to suit their needs. And it is also likely that ongoing advocacy and education will be required to ensure affordable, timely, and stigma-free access for all couples seeking to become parents.

**Shari Margolese is an HIV positive advocate living in Canada. She was recently awarded the Golden Jubilee Medal of Queen Elizabeth II for significant service to her community.**

### Selected sources

Al-Khan, A. and others. Assisted reproductive technology for men and women infected with human immunodeficiency virus type 1. *Clinical Infectious Diseases* 36(2): 195–200. January 15, 2003.

Chen, J.L. and others. Fertility desires and intentions of HIV-positive men and women. *Family Planning Perspectives* 33(4): 144–152. July 8, 2001.

# OPEN Clinical TRIALS

## FOR HIV/AIDS TREATMENTS



Below is a selection of currently enrolling U.S. clinical trials gathered from various sources. **TrialScope** is a database of organizations that conduct HIV/AIDS-related research. It provides contact information for each research site, links to organizational web sites, the types of research conducted by each site, and any affiliations with major multicenter research groups.

The federal government's **AIDSinfo** site includes a section on clinical trials. It features an introduction to HIV/AIDS research and study listings from the National Institutes of Health's **ClinicalTrials.gov** database. AIDSinfo also has a toll-free phone service at 800-874-2572. Specialists are on hand Monday through Friday from 12:00 pm to 4:00 pm ET (9:00 am to 1:00 pm PT) to help locate trials and answer questions. Like ClinicalTrials.gov, the **CenterWatch** web site also includes trial listings for all diseases including HIV/AIDS and related conditions.

**Community Programs for Clinical Research on AIDS (CPCRA)** is a nationwide network that conducts community-based clinical trials. **The AIDS Community Research Initiative of America (ACRIA)** provides a listing of trials mostly in the mid-Atlantic region (New York, New Jersey, Connecticut, and Pennsylvania).

**The Body** web site has created a new database of prospective clinical trial volunteers. The service collects information about participants' city, age, viral load, current and past anti-HIV therapy, and health status. Researchers can request information about prospective subjects, who will be contacted if they meet a trial's enrollment criteria. The application form is available at [www.thebody.com/redirect/trialapply.html](http://www.thebody.com/redirect/trialapply.html).

Call the telephone numbers listed for each study or see the indicated web sites for more information about specific trials. Protocol (study) numbers, if available, are provided in parentheses at the end of the trial descriptions.

**TrialScope:** [www.hivinsite.org/tscope](http://www.hivinsite.org/tscope)

**AIDSinfo:** [www.aidsinfo.nih.gov/clinical\\_trials](http://www.aidsinfo.nih.gov/clinical_trials)

**ClinicalTrials.gov:** [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

**CenterWatch:** [www.centerwatch.com](http://www.centerwatch.com)

**CPCRA:** [www.cpcra.org](http://www.cpcra.org)

**ACRIA:** [www.criany.org/clinical/index.html](http://www.criany.org/clinical/index.html)

## SMART: Drug Conservation vs Viral Suppression

The SMART study, conducted by the Community Programs for Clinical Research on AIDS (CPCRA), is a large, simple trial comparing two HIV treatment strategies. The study will attempt to determine whether participants at low risk of disease progression can safely reduce their use of antiretroviral therapy, thus minimizing side effects, slowing the development of drug resistance, and conserving future treatment options. Participants randomly assigned to the drug conservation arm will stop (or not start) anti-HIV therapy until their CD4 cell counts fall below 250 cells/mm<sup>3</sup>, at which point they will begin therapy and continue until their CD4 cell counts rise above 350 cells/mm<sup>3</sup>. Those assigned to the viral suppression arm will continue (or start) treatment in an attempt to keep viral load as low as possible, regardless of CD4 cell count. Some 6,000 participants will be followed for an estimated 6–9 years, until about 900 primary events (disease progression or death) occur. Selected participants will be followed with more intensive data collection for secondary outcomes related to cost, health-care utilization, metabolic complications, and quality of life.

Participants must be at least 13 years of age and have a CD4 cell count above 350 cells/mm<sup>3</sup> within 45 days of study entry. Subjects may be using any available

antiretroviral or immune-modulating drugs at study entry. They must be in reasonably good health and available to continue the study for at least six months. Women may not be pregnant or breast-feeding, and both female and male participants must be willing to use effective contraception.

There are more than 60 study sites, including **Atlanta** (404-876-2317 ext. 324), **Boston** (617-778-5454), **Brooklyn** (718-270-4487), **Chicago** (773-244-5802), **Denver** (303-436-7195), **Detroit** (313-745-4431), **Houston** (713-500-6751), **Los Angeles** (323-860-7330), **Miami** (305-324-4455 ext. 4942), **Newark** (973-483-3444), **New Orleans** (504-584-1971), **New York City** (212-939-2957), **Philadelphia** (215-707-8846 ext. 220), **Portland** (503-229-8428), **Richmond** (804-828-6471), **San Francisco** (415-476-9554 ext. 22), and **Washington, DC** (202-745-8301); [www.clinicaltrials.gov/ct/show/NCT00027352](http://www.clinicaltrials.gov/ct/show/NCT00027352) or [www.smart-trial.org](http://www.smart-trial.org). (CPCRA 065)

## First Therapy for Treatment-Naive Individuals

This study will evaluate the safety and effectiveness of combinations of approved antiretroviral drugs for HIV-positive individuals who have not received prior therapy. All subjects will be monitored at 12 scheduled clinic visits over a 48-week period and will have a follow-up visit or telephone call four weeks after the last study visit.

Eligible participants must be at least 18 years of age and may not have received antiretroviral therapy for more than 14 days in the past. Women may not be pregnant or breast-feeding and must agree to use birth control.

The study will be conducted at more than 50 sites, including **Atlanta** (770-431-4247), **Charlotte** (704-331-9054), **Chicago** (773-702-1209), **Cleveland** (216-444-0214), **Dallas** (214-941-4000), **Denver** (303-764-4776), **Los Angeles** (310-550-1010), **Miami** (305-243-5621), **Newark** (973-877-2595), **New Orleans** (504-903-7890), **Philadelphia** (215-707-8846), **San Francisco** (415-221-4810, ext. 763), and **St. Louis** (314-454-1931); [www.clinicaltrials.gov/ct/show/NCT00082394](http://www.clinicaltrials.gov/ct/show/NCT00082394). (ESS100327)

## Once-Daily vs Twice-Daily HAART and DOT

This open-label Phase II study will compare once-daily vs twice-daily administration of antiretroviral drugs, and will also look at self-administered vs directly observed therapy (DOT). The trial is for people who are taking anti-HIV therapy for the first time. Participants will be randomly assigned to one of three study arms. All will receive the same daily dosages of lopinavir (Kaletra), emtricitabine (FTC, Emtriva), and extended-release d4T

(stavudine, Zerit). Participants in Arm A will self-administer lopinavir twice daily, and emtricitabine and d4T once daily for 48 weeks. Arm B participants will self-administer all three drugs once daily for 48 weeks. Those in Arm C will take all three drugs once daily in the presence of a clinician for 24 weeks, then by self-administration for 24 additional weeks. The study will measure safety, efficacy, tolerability, and quality of life.

Participants must be at least 13 years of age and have a viral load of at least 2,000 copies/mL within 90 days of study entry. They must not have taken any antiretroviral drugs for more than seven days. Participants are ineligible if they have recently had certain illnesses or taken certain medications, including those that may cause pancreatitis (inflammation of the pancreas) or peripheral neuropathy. Women may not be pregnant or breast-feeding, and both female and male participants must use effective contraception.

There are more than 20 sites, including **Baltimore** (410-614-4487), **Cleveland** (216-778-5489), **Denver** (303-372-5535), **Indianapolis** (317-274-8456), **Miami** (305-243-3838), **New York City** (212-263-6565), **Philadelphia** (215-349-8092), **Providence** (401-793-4396), **Rochester** (585-275-2740), **Sacramento** (916-734-8637), **San Juan** (787-767-9192), and **Seattle** (206-731-8877); [www.clinicaltrials.gov/ct/show/NCT00036452](http://www.clinicaltrials.gov/ct/show/NCT00036452). (ACTG A5073)

## When to Start HAART in People with OIs

This study will attempt to determine when is the best time to start antiretroviral therapy in individuals presenting with opportunistic illnesses (OIs). Immediately starting HAART may be disadvantageous and anti-HIV medications can interact with drugs used to treat OIs. This trial will compare the benefits and drawbacks of starting antiretroviral therapy immediately vs waiting until after OI treatment is underway or completed. Participants will be randomly assigned either to begin antiretroviral therapy within two months of starting OI treatment (Arm A), or to defer anti-HIV treatment until at least four weeks—but no more than 32 weeks—after beginning OI therapy. All subjects will receive lopinavir plus d4T, and may also receive a third and fourth anti-HIV drug at the discretion of study clinicians. The study will last 48 weeks and participants will have ten study visits, which will include blood tests, physical examinations, and questionnaires.

Eligible participants must be at least 13 years of age. They must have a confirmed or suspected acute OI, including *Pneumocystis carinii* pneumonia (PCP), bacterial pneumonia, cryptococcal meningitis, disseminated histoplasmosis, disseminated *Mycobacterium avium* complex (MAC), cytomegalovirus (CMV) retinitis or encephalitis, or toxoplasmic encephalitis. Participants may not have been on

antiretroviral therapy within six months of study entry or for a total of six months at any time prior to joining the study, and may not have been treated for their current OI for more than 14 days prior to study entry. Certain medical conditions and recent use of certain medications are excluded. Women may not be pregnant or breast-feeding, and all subjects must be willing to use effective contraception.

The study will enroll 282 participants at more than 20 sites, including **Boston** (617-732-5635), **Chapel Hill** (919-843-8761), **Denver** (303-372-5535), **Galveston** (409-747-0241), **Indianapolis** (317-274-8456), **Miami** (305-243-3838), **New York City** (212-305-2665), **Rochester** (585-275-2740), **San Francisco** (415-514-0550 ext. 354), **Stanford** (650-723-2804), and **St. Louis** (314-454-0058); [www.clinicaltrials.gov/ct/show/NCT00055120](http://www.clinicaltrials.gov/ct/show/NCT00055120). (ACTG A5164)

## Tipranavir Open-Label Study

Boehringer Ingelheim has expanded its open-label safety study of tipranavir, an investigational nonpeptidic protease inhibitor (PI) currently in Phase III development. The expanded study, part of the company's RESIST program, has broader enrollment criteria and twice the number of study sites, and will allow 50 more individuals per month to participate. The nonrandomized open-label study is for individuals who are failing or unable to tolerate their current therapy and need a new PI to construct a viable regimen. All subjects will receive 500 mg tipranavir plus 200 mg ritonavir (Norvir) twice daily; there is no placebo arm.

Prospective subjects must be at least 13 years of age and must be failing to achieve virological suppression on their current regimen, with a CD4 cell count of 100 cells/mm<sup>3</sup> or less and a viral load of 10,000 copies/mL or more. They must not have certain medical conditions (including liver impairment) and may not be taking certain drugs. Women may not be pregnant or breast-feeding and must agree to use a barrier method of contraception. Participants may not join the open-label study if they are eligible for another tipranavir trial in their area.

The open-label study is being conducted at more than 60 sites, including **Atlanta, Baltimore, Boston, Chicago, Cincinnati, Detroit, Houston, Las Vegas, Los Angeles, Madison, Nashville, Newark, New Orleans, New York City, Philadelphia, San Francisco, Santa Fe, Seattle, St. Louis, Tampa, and Washington, DC**. For more details and local contact information, call the Boehringer Ingelheim study hotline at 800-632-2464; [www.clinicaltrials.gov/ct/show/NCT00062660](http://www.clinicaltrials.gov/ct/show/NCT00062660). (BI 1182.58)

## New Entry Inhibitor: SCH-D

This Phase II study will examine the safety and effectiveness of a new oral entry inhibitor, Schering-Plough's SCH-D (also known as SCH 417690), in treatment-experienced individuals whose current antiretroviral

regimens are failing. SCH-D targets the CCR5 receptor on human cells and prevents HIV from entering (see "Drug Watch" on page 14). Participants will be randomly assigned to receive one of three different doses of the drug (5 mg, 10 mg, or 15 mg) or placebo daily for 48 weeks. Subjects will also remain on their current anti-HIV drugs, which are not provided by the study; after two weeks, participants will begin an optimized antiretroviral regimen based on the results of genotypic/phenotypic resistance testing. Study visits with blood draws will take place on day 4 and at weeks 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48. Subjects will also undergo electrocardiograms (EKGs) at weeks 2, 8, 24, and 48, and will be tested for peripheral neuropathy.

Prospective subjects must be at least 18 years of age and must be experiencing virological failure on their current antiretroviral regimen (HIV viral load of at least 5,000 copies/mL within six weeks of study entry). The current regimen must include ritonavir, and must have been stable for at least eight weeks prior to study entry. Participants will be tested to ensure that they have a type of HIV that uses CCR5 (not CXCR4) coreceptors. Subjects may not have taken efavirenz (Sustiva) or nevirapine (Viramune) within eight weeks of study entry, or certain other medications (including immunosuppressants, immune modulators, or cancer chemotherapy) within the past 30 days. They may not have hepatitis B or C coinfection or a history of seizures. Women may not be pregnant or breast-feeding, and all participants must be willing to use effective contraception.

The study will enroll participants at 15 U.S. study sites, including **Boston** (617-414-7082), **Honolulu** (808-737-2751), and **New York City** (212-476-4393), and **Stanford** (650-723-2804); [www.clinicaltrials.gov/ct/show/NCT00082498](http://www.clinicaltrials.gov/ct/show/NCT00082498). (ACTG A5211)

## New NRTI: D-D4FC

This double-blind Phase II trial will explore the safety, tolerability, and efficacy of D-D4FC (Reverset; see "Drug Watch" on page 13), a new nucleoside reverse transcriptase inhibitor (NRTI). Treatment-experienced subjects will receive 50, 100, or 200 mg doses of D-D4FC, or placebo, once daily in combination with other antiretroviral drugs. At week 2, participants' regimens will be optimized based on the results of genotypic resistance testing; further reoptimization may be done at week 16. Also at week 16, those initially randomized to receive placebo will begin receiving 100 or 200 mg of D-D4FC. After 24 weeks, selected participants will have the option to enroll in an extension study.

Eligible subjects must be adults experiencing virological failure on their current regimens, with a viral load of at least 2,000 copies/mL and a CD4 cell count greater than 50 cells/mm<sup>3</sup>.

Study sites include **Baltimore** (410-614-1338), **Boston** (617-778-5454 ext. 223), **Chicago** (312-695-5045),

**Ft. Lauderdale** (954-524-2250), **Galveston** (409-747-0203), **Houston** (713-526-9821), **Los Angeles** (323-343-8283), **Miami** (305-243-3838), **New York City** (212-420-4519), **San Francisco** (415-476-9296 ext. 303), **Tampa** (813-307-8015 ext. 6443), and **Washington, DC** (202-741-2443). (INCB 8721 RVT-203)

## Ribozyme Gene Therapy

This study will explore whether gene therapy can alter immune system white blood cells so they can better fight HIV. In this study, a gene encoding a ribozyme (a type of enzyme) will be inserted into blood-forming stem cells, and the cells will be returned to the body. As the stem cells give rise to new white blood cells such as macrophages and T cells, the researchers hope that the ribozyme inside the cells will destroy HIV. Participants will be randomly assigned to receive the ribozyme gene or a “dummy” gene. The National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA) have reviewed the study and believe the procedure is safe.

Prospective participants must be 18–45 years of age and on their first or second anti-HIV regimen. They must have well-controlled HIV, with a viral load of 400 copies/mL or less and a CD4 cell count of at least 300 cells/mm<sup>3</sup>. Pregnant women and individuals with a history of AIDS-defining illness are not eligible.

The study will enroll 70 participants in **Los Angeles** (310-794-9668), **Stanford** (650-723-6231), and a center in **Sydney, Australia**.

## Blood Sugar Abnormalities in Pregnant Women

This study will look at the incidence of blood sugar abnormalities in HIV positive pregnant women taking antiretroviral therapy. The trial will enroll 160 women, who will be followed every eight weeks from study entry through delivery, with a final visit 12 weeks after delivery. Glucose tolerance tests and other metabolic measurements will be performed. Newborn infants will also be evaluated at birth and at 12 weeks of age. This is an observational study of women already using anti-HIV therapy; drugs will not be provided.

Eligible women must be at least 13 years of age and be 20–24 weeks pregnant at study entry. They must have been on stable antiretroviral therapy including a PI for the eight weeks immediately prior to joining the study, and must plan to continue that regimen throughout the trial. Participants are not eligible if they currently have diabetes, although they may have a history of blood sugar problems during past pregnancies. Participants may not have a recent serious medical condition or have recently used certain medications, including steroids or drugs to control blood sugar or blood lipids (fats).

The study will be conducted at nearly 40 sites including **Baltimore** (410-706-8933), **Birmingham** (205-558-2328), **Boston** (617-732-5635), **Chicago** (773-257-5717), **Cleveland** (216-844-8051), **Detroit** (313-745-7857), **Durham** (919-684-8216), **Honolulu** (808-737-2751), **Indianapolis** (317-274-8456), **Los Angeles** (323-226-2342), **Miami** (305-243-2154), **Minneapolis** (612-625-1462), **Nashville** (615-467-0154 ext. 105), **Newark** (973-972-3118), **New York** (212-263-6565), **Pittsburgh** (412-647-0771), **San Juan** (787-765-4186), **Seattle** (206-528-5020), **St. Louis** (314-454-0058), and **Washington, DC** (202-865-4578); [www.clinicaltrials.gov/ct/show/NCT00017797](http://www.clinicaltrials.gov/ct/show/NCT00017797). (ACTG A5084)

## Metabolic Abnormalities in Young Women

This study will look at metabolic complications in young women with HIV, including abnormal blood glucose and lipid levels, body fat changes, and bone density alterations. The study will compare metabolic parameters in HIV negative women, HIV positive women who have never used HAART, and HIV positive women taking regimens that include non-nucleoside reverse transcriptase inhibitors (NNRTIs) but no PIs, PIs but no NNRTIs, or neither PIs nor NNRTIs. In this cross-sectional observational study, participants will be seen just one time; the visit will include a questionnaire, a DEXA scan to assess body composition, and blood tests to measure glucose, lipid, and lactic acid levels.

Eligible women must be 12–24 years of age. Both HIV negative and HIV positive participants are needed, and those with HIV may be taking any type of antiretroviral therapy, or not be on treatment at all. Subjects are not eligible if they have type 1 diabetes or type 2 diabetes that must be controlled with daily medication. Participants may not be pregnant currently or within the past year.

Study sites include **Chicago** (312-572-4571), **Los Angeles** (323-660-2450 ext. 3914), **Miami** (305-243-3442), **New Orleans** (504-588-5348), **New York** (212-423-2867), **Philadelphia** (215-590-4954), **San Diego** (619-543-8080), **Tampa** (813-259-8799), and **Washington, DC** (202-884-3714); [www.clinicaltrials.gov/ct/show/NCT00067587](http://www.clinicaltrials.gov/ct/show/NCT00067587). (ATN 021)

## Metabolic Abnormalities in Children and Youth

This study will examine the prevalence of metabolic and physical abnormalities in HIV positive children, adolescents, and young adults who were infected via mother-to-child transmission. Metabolic parameters, body composition, bone density, and other factors will be assessed to see whether there is an association with antiretroviral therapy. The trial will include three groups: HIV positive

children and youth receiving antiretroviral regimens containing PIs, HIV positive subjects taking PI-sparing regimens, and an HIV negative control group. Participants will receive blood tests and whole-body DEXA scans to assess bone density.

Eligible participants must be 7–25 years of age. Both HIV positive and negative subjects are needed. HIV positive subjects in the PI group must have been on a stable PI-containing regimen for at least 12 months, while the PI-sparing group must not have used a PI within 12 months of study entry and must not have been exposed to PIs for more than two weeks in the past. Participants may not have type 2 diabetes that must be controlled with drugs and may not be taking certain medications including growth hormone, glucocorticoids, or anabolic steroids. Female subjects may not be pregnant currently or within the past year.

The study is expected to enroll 450 participants at about 20 sites, including **Birmingham** (205-558-2328), **Boston** (617-355-8198), **Denver** (303-861-6751), **Detroit** (313-745-7857), **Los Angeles** (323-226-2226), **Memphis** (901-495-3490), **Newark** (973-972-3118), **New York City** (212-939-4045), **Oakland** (510-428-3885 ext. 2827), **Philadelphia** (215-427-5284), **San Diego** (619-543-8080), and **San Francisco** (415-476-6480); [www.clinicaltrials.gov/show/NCT00069004](http://www.clinicaltrials.gov/show/NCT00069004). (PACTG P1045)

## Metformin and Rosiglitazone for Lipid and Insulin Abnormalities

This double-blind trial will evaluate the effect of metformin (Glucophage) and rosiglitazone (Avandia), taken alone or in combination, on elevated insulin levels and body fat accumulation in the abdomen and other areas. Metformin and rosiglitazone are currently FDA-approved for these indications in HIV negative people. Participants will be randomly assigned to receive either metformin plus rosiglitazone placebo, rosiglitazone plus metformin placebo, metformin plus rosiglitazone, or placebos of both drugs. After 16 weeks participants who remain in the study will be switched to an open-label phase and all will receive metformin plus rosiglitazone for an additional 16 weeks. Clinic visits will take place at weeks 2, 4, 8, 12, 16, 18, 20, 24, 28, and 32, and will include blood draws to assess insulin and glucose levels (this must be done after fasting overnight). In addition, visceral (internal) fat, subcutaneous fat, and thigh size will be measured.

Participants must be 18–65 years of age and have a viral load below 10,000 copies/mL within 30 days of study entry. They must have specific blood insulin levels and meet physical restrictions based on height, weight, and amount and location of body fat. Subjects must be on a stable anti-HIV regimen for at least 60 days prior to study entry. Participants may not have previously taken drugs to control blood sugar. They may not be taking ritonavir with

either simvastatin (Zocor) or lovastatin (Mevacor). Subjects are ineligible if they have certain medical conditions or have recently taken certain medications. Women may not be pregnant or breast-feeding, and all participants must be willing to use effective contraception.

There are more than 30 study sites, including **Baltimore** (410-614-4487), **Birmingham** (205-975-7925), **Boston** (617-726-3819), **Chapel Hill** (919-843-8761), **Chicago** (312-695-5012), **Cincinnati** (513-584-8373), **Denver** (303-372-5535), **Honolulu** (808-737-2751), **Indianapolis** (317-274-8456), **Los Angeles** (310-206-8029), **Nashville** (615-467-0154 ext. 109), **New York** (212-420-4432), **Omaha** (402-559-8163), **Pittsburgh** (412-647-0771), **San Francisco** (415-514-0550 ext. 362), **Seattle** (206-731-8877), **St. Louis** (314-454-0058), and **Washington, DC** (202-687-5378); [www.clinicaltrials.gov/ct/show/NCT00015691](http://www.clinicaltrials.gov/ct/show/NCT00015691). (ACTG A5082)

## Oyster Mushrooms for Hyperlipidemia

This open-label “proof of concept” study will evaluate the short-term safety and potential efficacy of oyster mushrooms for the treatment of elevated blood fats (hyperlipidemia) in HIV positive subjects taking lopinavir. Participants will take freeze-dried oyster mushroom powder, which can be added to soup or other foods, once daily for eight weeks. Subjects will have two overnight stays at San Francisco General Hospital, during which blood will be drawn several times, plus three outpatient visits; they will be reimbursed \$50 for each overnight stay and \$25 for each outpatient visit.

Eligible participants must be at least 18 years of age and must have been taking lopinavir for at least 12 weeks. They must have an elevated non-HDL cholesterol level (at least 190 mg/dL) and normal liver function tests within 30 days of study entry. Prospective subjects may not currently be using lipid-lowering drugs, and may not have diabetes, rhabdomyolysis (a type of muscle damage), or certain other medical conditions. Women may not be pregnant or breast-feeding.

The study will enroll 20 participants in **San Francisco** (415-476-9554 ext. 315); [www.clinicaltrials.gov/ct/show/NCT00069524](http://www.clinicaltrials.gov/ct/show/NCT00069524). (AT001782-01)

## Testosterone for Men with Lipodystrophy

This double-blind study will examine whether testosterone supplements can help reduce abdominal fat accumulation in HIV positive men with low testosterone levels (hypogonadism) taking antiretroviral therapy. Testosterone has been shown to decrease abdominal fat in HIV negative men (see “HIV and Hormones” on page 34). Participants

will receive either testosterone gel or a placebo gel applied to the skin once daily for 24 weeks. Those who receive testosterone during the first 24 weeks will be eligible to continue therapy for 24 more weeks. Those receiving placebo gel will be followed for an additional 24 weeks. All subjects will remain on their current antiretroviral regimens. Tests for visceral fat changes will be performed throughout the study period.

HIV positive men 18–70 years of age are eligible for this study. Participants must have been on anti-HIV therapy for at least 12 weeks before study entry and plan to continue for at least 24 additional weeks. They must have an abdominal girth of at least 100 cm (39.4 inches), with an increase since starting HAART. Viral load must be less than 10,000 copies/mL and total serum testosterone must be 125–400 ng/dL. Subjects may not have diabetes, cancer, active OIs, or certain other medical conditions, and must not be taking certain drugs including testosterone derivatives, anabolic steroids, DHEA, glucocorticoids, antidiabetes medications, dronabinol (Marinol), megestrol acetate (Megace), or growth hormone.

A total of 86 participants will be enrolled at more than 20 study sites, including **Chicago** (312-695-501), **Denver** (303-372-5535), **Honolulu** (808-737-2751), **Indianapolis** (317-274-8456), **Minneapolis** (612-625-1462), **New York City** (212-263-6565), **Philadelphia** (215-349-8092), **San Diego** (619-543-8080), **San Francisco** (415-514-0550 ext. 362), **San Juan** (787-767-9192), and **St. Louis** (314-454-0058); [www.clinicaltrials.gov/show/NCT00009555](http://www.clinicaltrials.gov/show/NCT00009555). (ACTG A5079)

## Testosterone for Premenopausal Women with Wasting

This study will examine whether physiological testosterone supplements that bring testosterone levels up into the normal natural range can increase lean body weight, improve muscle function, and improve quality of life in women with HIV. Participants will be randomly assigned to use two testosterone skin patches, one testosterone and one placebo patch, or two placebo patches applied twice weekly (every 3–4 days) for 12 weeks.

Prospective participants must be premenopausal women aged 18–50 years. They must have experienced weight loss of 5–15% and must have a total testosterone level less than 30 ng/dL. Subjects may be taking any stable antiretroviral regimen, and must not have used any anabolic or androgenic steroids or hormonal contraceptives for three months. Hormone replacement therapy (HRT) is not allowed. Exclusion criteria also include significant liver or cardiovascular disease, uncontrolled high blood pressure, active OIs, diabetes, use of street drugs within the past six months, and pregnancy and/or breast-feeding.

The study will enroll 56 women in **Los Angeles** (213-563-9353) and **St. Louis** (314-222-2444); [www.clinicaltrials.gov/ct/show/NCT00004400](http://www.clinicaltrials.gov/ct/show/NCT00004400). (199/13251; CDUMS-FDR001397)

## Growth Hormone to Reduce Abdominal Fat

This Phase III study, sponsored by Serono, will assess the use of recombinant human growth hormone (Serostim) as a treatment for visceral fat accumulation and abnormal body fat distribution. Participants will be randomly assigned to receive either 4 mg of Serostim or placebo daily for 12 weeks.

Prospective subjects must be 18–60 years of age; both men and women are eligible. They must have evidence of excess abdominal fat (waist circumference greater than 88.2 cm, or 34.7 inches, and waist-to-hip ratio of at least 0.95 for men; waist circumference greater than 75.3 cm, or 29.6 inches, and waist-to-hip ratio of at least 0.9 for women). Subjects may be taking any stable regimen of approved antiretroviral drugs and must agree to remain on the same regimen for the duration of the study unless a change is medically necessary. Participants must have liver enzyme, triglyceride, and glucose levels within the normal range. They may not have active OIs, untreated high blood pressure, or a history of diabetes, cancer, pancreatitis, coronary artery disease, or certain other medical conditions. They may not be taking certain medications including antidiabetes drugs, interferon, glucocorticoids, or androgenic agents such as testosterone. Women may not be pregnant or breast-feeding and must agree to use effective contraception.

Study sites include **Atlanta** (404-876-2317 ext. 336), **Austin** (512-480-9660), **Birmingham** (205-975-9127), **Boston** (617-636-0492), **Chicago** (312-942-5000 ext. 29156), **Ft. Lauderdale** (954-524-2250), **New York City** (212-523-3671), **Palm Springs** (760-325-4590), and **West Hollywood** (310-358-2429); [www.clinicaltrials.gov/ct/show/NCT00082628](http://www.clinicaltrials.gov/ct/show/NCT00082628). (24380)

## Growth Hormone and Immune Function

This study will examine how growth hormone (GH) influences immune function in people with HIV. Research has shown that GH promotes the growth of the thymus gland, an important site of T cell production in children and possibly adults. The study will assess whether growth hormone induces thymus growth and a consequent increase in T cell proliferation. Participants will be followed for two years. One arm will receive GH by subcutaneous injection during the first 12 months (3 mg daily for the first six months, then reduced to 1.5 mg daily). The other arm will be observed for the first 12 months and then begin receiving GH during the second year. Study visits, which will take place about every 1–3 months, will include physical exams, blood tests, and different types of body scans (CT, PET, DEXA).

Eligible participants must be at least 18 years of age and must be taking at least two antiretroviral drugs. They must have a CD4 cell count of 400 cells/mm<sup>3</sup> or less and a viral load less than 1,000 copies/mL for one year prior to study entry. They may not have diabetes, cancer, some forms of heart disease, or carpal tunnel syndrome. Women may not be pregnant or breast-feeding.

The study will enroll 24 participants in **San Francisco** (415-695-3820); [www.clinicaltrials.gov/ct/show/NCT00071240](http://www.clinicaltrials.gov/ct/show/NCT00071240). (R01; A143864)

## Endothelial Dysfunction

This study will look at whether endothelial (blood vessel lining) changes are a risk factor for cardiovascular disease in people taking HAART. It will also evaluate the effect of three different medications on blood lipid levels and insulin resistance. Participants will receive pravastatin (Pravachol), gemfibrozil (Lopid), rosiglitazone (Avandia), or a placebo for six weeks; those who started on an active drug will later be switched to a placebo, and vice versa. Blood assays and endothelial function tests will be performed throughout the study.

Prospective participants must be at least 18 years of age and have been on stable antiretroviral therapy for at least two months preceding study entry. They must not smoke more than a pack per day of cigarettes and must abstain from caffeine during the study. Subjects may not have a history of coronary artery disease, heart failure, myocardial infarction (heart attack), high blood pressure, liver or kidney disease, or diabetes, and may not be taking certain medications. Women must not be pregnant or breast-feeding and all participants must be willing to use a barrier method of contraception.

The study will enroll 75 participants in **Bethesda** (301-435-7913); [www.clinicaltrials.gov/ct/show/NCT00039663](http://www.clinicaltrials.gov/ct/show/NCT00039663). (02-CC-0208)

## Medical Marijuana for Peripheral Neuropathy

This study will assess whether smoked marijuana (cannabis) helps relieve pain related to peripheral neuropathy, a potential side effect of certain antiretroviral drugs. A recently completed pilot study showed that medical cannabis is effective for this indication; the current study will extend the research to a larger number of participants. Subjects will be housed at San Francisco General Hospital for seven days, where they will be randomly assigned to smoke either marijuana or placebo cigarettes three times daily. A heat/capsaicin (hot pepper) pain test will be administered at the beginning of the study and at the end of the inpatient stay. Participants who complete the study will be compensated \$650.

Prospective participants must be at least 18 years of age and have painful HIV-related neuropathy. They must

either not be taking antiretroviral medications or have been on stable therapy for at least the past eight weeks. They must have used marijuana on at least six occasions in the past, but not within the 30 days prior to study entry. There are no CD4 cell count or viral load requirements. Subjects may not have diabetes, uncontrolled high blood pressure, or heart or lung disease, and must not be using certain medications including corticosteroids. Current tobacco users are not eligible. Women may not be pregnant or breast-feeding.

The study will enroll 50 participants in **San Francisco** (415-476-9554 ext. 366); [www.clinicaltrials.gov/ct/show/NCT00046722](http://www.clinicaltrials.gov/ct/show/NCT00046722). (CC 056)

## Can Herpes Suppression Prevent HIV?

The ACE study, conducted by the San Francisco Department of Public Health, will examine whether suppression of genital herpes (herpes simplex virus type 2, or HSV-2) with acyclovir (Zovirax) can help reduce the risk of contracting HIV. Research to date indicates that having even subclinical HSV-2 infection without obvious lesions can increase the likelihood that an individual will contract or transmit HIV. Participants will be randomly assigned to receive either 400 mg of acyclovir or placebo twice daily for 12 months. Those who develop genital herpes outbreaks will be treated with open-label acyclovir. Study visits will take place every month and participants will be compensated for their time.

Eligible participants are sexually active HIV negative gay or bisexual men at least 18 years of age with confirmed HSV-2 infection.

The study will enroll 315 participants in **New York City** (212-388-0008), **San Francisco** (415-554-9064), and **Seattle** (206-521-5821).

### Lifestyle Habits That Contribute to Optimal Health

- Eat a low-fat diet based on fruits, vegetables, and whole grains
- Exercise daily for at least 30 minutes
- Sleep at least eight hours every night
- Avoid smoking and second-hand smoke
- Reduce alcohol intake

**CAN YOU HELP MAKE GOVERNMENT DO  
THE RIGHT THING ABOUT HIV/AIDS?**

# You Can by Joining HAN.



The HIV Advocacy Network (HAN) is the grassroots community-organizing program of the San Francisco AIDS Foundation. HAN organizes people living with and affected by HIV/AIDS, HIV service providers, and advocates to promote sound public policy to speed the epidemic to an end.

Through HAN, you can be directly involved in activities including rallies, letter writing, and phone calling that will influence government decisions about funding and legislation related to HIV and AIDS. You will receive regular updates about the most pressing public policy issues for the community.

With more than 1,200 members, HAN is a respected voice in HIV/AIDS advocacy at the federal, state, and local levels. HAN has a proven track record of success in promoting policies that help people affected by HIV. Most recently, HAN members successfully persuaded Governor Schwarzenegger to substantially increase funding for the California AIDS Drug Assistance Program (ADAP) in the 2004–2005 budget.

**ONE VOICE REALLY DOES MAKE A DIFFERENCE. BECOME A MEMBER OF HAN TODAY.**

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policy@sfaf.org

NAME: \_\_\_\_\_

ORGANIZATION: \_\_\_\_\_

ADDRESS: \_\_\_\_\_

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