

Bulletin of Experimental Treatments for AIDS

BETA

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Salvage Therapy
17

**HIV and
Hepatitis
Coinfection**
32

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Editor

Nicholas Cheonis

Copy Editor

Liz Highleyman

Proofreader

Leslie Hanna

**Design and
Production Manager**

Paula Fener

**Contributors to
this Issue**

Nicholas Cheonis

Simon Collins

Leslie Hanna

Liz Highleyman

Bob Roehr

**Scientific Advisory
Committee**

Kirsten Balano, PharmD

George Beatty, MD, MPH

Eric Goosby, MD

Gregory Pauxtis, MD

Photography

Photodisc.com

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Editorial address:

PO Box 426182
San Francisco, CA 94142-6182

Telephone: 415-487-8060

Fax: 415-487-8069

Web: www.sfaf.org/beta

E-mail: beta@sfaf.org

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notice

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Editor's Note

Is AIDS a manageable disease like diabetes, as some have suggested over the past few years? It may have the potential to be so, using strategies to maximize the usefulness of current drugs (see page 17) and new therapies in the research pipeline, as reported in the last issue. Yet the reality of HIV disease often brings to mind crisis management rather than a vision of long-term control. Side effects of anti-HIV agents—not to mention the effects of the disease itself—can complicate any treatment plan. Reports from recent conferences (see page 4) confirm a lack of understanding of drug side effects, although novel ways of treating them are being looked at (see page 12). For people coinfecting with hepatitis C or B it can be harder still to manage HIV disease. Research continues in this area, however, and new

agents for viral hepatitis have recently been approved (see page 32). In addition, interviews with clinicians and treatment advocates suggest that many complex issues specific to women with HIV have yet to be adequately addressed (see page 29).

As the new editor of *BETA*, I know from my years on this journal's editorial staff that the most important service we can provide is accurate, in-depth, and freely accessible HIV health information. The best means of assessing the work we do has always been for readers to provide us with feedback. Some data from our recent reader survey are included below. I encourage all our readers to keep the comments coming.

Nicholas

Nicholas Cheonis

2002

BETA READER SURVEY RESULTS

OF THE MORE THAN 5,000 INDIVIDUAL AND INSTITUTIONAL SUBSCRIBERS TO *BETA*, 340 (7%) RESPONDED TO THE READER SURVEY PUBLISHED IN THE SPRING 2002 ISSUE.

- 90% WERE OVER THE AGE OF 35
- 27% BELONGED TO AN ETHNIC MINORITY GROUP
- 66% WERE GAY/LESBIAN, 21% WERE HETEROSEXUAL, AND 13% WERE BISEXUAL
- 34% HAD AN INCOME BELOW \$15,000 PER YEAR
- 14% HAD NEVER ATTENDED COLLEGE
- 84% WERE HIV POSITIVE—OF THESE, 70% HAD BEEN HIV POSITIVE FOR MORE THAN TEN YEARS AND 55% WERE TAKING AT LEAST THEIR THIRD ANTIRETROVIRAL REGIMEN.

THE THREE MOST COMMON CONCERNS WERE DRUG-RELATED SIDE EFFECTS, LIPODYSTROPHY, AND DEPRESSION OR ANXIETY. RESPONDENTS WERE MOST LIKELY TO READ THE DRUG WATCH AND NEWS BRIEFS COLUMNS. NOTABLY, 20% WISHED TO SEE MORE ARTICLES PER ISSUE AND 95% DID NOT READ *BETA* ONLINE.

A COMPREHENSIVE REPORT OF THE 2002 READER SURVEY RESULTS IS AVAILABLE ON THE *BETA* WEB SITE (WWW.SFAF.ORG/BETA).

Liz Highleyman

FOR THE LATEST UPDATED TREATMENT GUIDELINES FOR ADULTS, ADOLESCENTS, CHILDREN, AND PREGNANT WOMEN; POSTEXPOSURE PROPHYLAXIS (PEP) GUIDELINES FOR OCCUPATIONAL AND NONOCCUPATIONAL EXPOSURE; AND OPPORTUNISTIC ILLNESS (OI) PREVENTION GUIDELINES, VISIT WWW.AIDSINFO.NIH.GOV.

Conference Highlights

Several important HIV/AIDS conferences have taken place in the past several months, including the XIV International AIDS Conference (Barcelona, Spain, July 7–12), the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV (San Diego, September 22–25), and the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC, San Diego, September 27–30).

The International AIDS Conference focused largely on global issues. Topics of note included treatment interruption (see below), short-course treatment, delays in starting therapy (see below), HIV superinfection (see below), new pipeline drugs, heart disease in people with HIV, and drug-resistant HIV. Both former U.S. president Bill Clinton and former South African president Nelson Mandela spoke of the need for increased funding for HIV prevention and treatment in poor countries. The mood of the conference was somber as participants acknowledged the magnitude of the global epidemic and the fact that there is no AIDS cure or vaccine on the horizon.

Several studies presented at ICAAC looked at simpler regimens that may help improve adherence. Michael Saag, MD, of the University of Alabama at Birmingham presented promising results from a trial comparing the experimental once-daily nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine (FTC, Coviracil) with d4T (stavudine, Zerit) in combination regimens. Results for emtricitabine were so good, in fact, that the trial's Data and Safety Monitoring

Board (DSMB) decided to end the study early. In September manufacturer Triangle Pharmaceuticals submitted a New Drug Application (NDA) for emtricitabine (see below). Once-daily dosing of 3TC (lamivudine, Epivir) also appears promising.

Adding low-dose ritonavir (Norvir) to a regimen containing another protease inhibitor (PI) can help reduce pill burden and frequency of dosing. Gilles Raguin, MD, from Hôpital Saint-Antoine in Paris and colleagues reported that adding ritonavir increased the effectiveness of regimens containing amprenavir (Agenerase) or lopinavir (Kaletra); Kaletra is already formulated with a small amount of ritonavir. In this study, adding extra ritonavir further boosted PI drug levels without significantly increasing side effects.

Several studies looked at new drugs. Kathleen Squires, MD, of the University of Southern California in Los Angeles presented some promising data on the new PI atazanavir (Zrivada). GlaxoSmithKline's GW433908, or simply 908—a prodrug of amprenavir—appears effective and requires fewer pills each day. In the NEAT trial, after 24 weeks of therapy 54% of participants taking 908 and 40% of those taking nelfinavir (Viracept) achieved viral loads below 50 copies/mL. Other studies looked at anti-HIV drugs that work by novel mechanisms. Data were presented for TMC-125 (a non-nucleoside reverse transcriptase inhibitor, or NNRTI), TMC-114 (a PI), PRO 542 (an entry inhibitor), and S291 and N36E (two new peptide entry inhibitors). CCR5 receptor blockers and integrase inhibitors are further back in the drug development pipeline. (For more information on new drugs, see “The HIV/AIDS Drug Pipeline: A Status Report,” *BETA*, Summer/Autumn 2002, page 29).

Side effects of antiretroviral therapy were another major theme, especially lipodystrophy, elevated blood lipid (fat) levels (hyperlipidemia), and mitochondrial toxicity. The new PI atazanavir appears less likely than other drugs in its class to cause blood lipid elevations. Several researchers have conducted “switch studies” and tested regimens that “spare” (omit) certain drug classes in the hope of minimizing adverse effects. Many have explored protease-sparing regimens to reduce blood lipid elevations.

A report at the Barcelona AIDS conference showed that an initial regimen of efavirenz (Sustiva), AZT (zidovudine, Retrovir), and 3TC was as effective as a regimen of nelfinavir, ddI (didanosine, Videx), and d4T, but was associated with fewer side effects. Many studies have shown that efavirenz (an NNRTI) is associated with less hyperlipidemia than nelfinavir (a PI). But atazanavir may produce even less hyperlipidemia than efavirenz; in one study, triglyceride levels actually decreased in those taking this drug. Switching from PIs to efavirenz reduced blood fat levels in children as well as adults.

Several studies at ICAAC looked at treating hyperlipidemia in people using highly active antiretroviral therapy (HAART). In this population, lifestyle changes such as exercise and diet modification led to only modest improvements, and maintaining these changes was a problem. A

study comparing the lipid-lowering drugs fenofibrate (TriCor), bezafibrate (Bezalip), pravastatin (Pravachol), and atorvastatin (Lipitor) found that both the fibrates and the statins reduced triglyceride and cholesterol levels by similar amounts, indicating that a variety of drugs can be used successfully to treat hyperlipidemia in people with HIV.

At the Workshop on Adverse Drug Reactions and Lipodystrophy, Jeffrey Friedman, MD, of The Rockefeller University in New York City gave a keynote lecture on the possible role of leptin in treating lipodystrophy. Leptin is a natural hormone produced by adipose (fat) tissue that regulates fat and glucose metabolism. A report by Elif Arioglu Oral, MD, of the National Institute of Diabetes and Digestive and Kidney Diseases and colleagues in the February 21, 2002 issue of the *New England Journal of Medicine* described the use of leptin replacement therapy in HIV negative people with lipodystrophy. Two other abstracts at the workshop looked at the role of adiponectin, another hormone produced by fat cells, in people with HIV-related lipodystrophy and insulin resistance. Researchers are just beginning to explore the possibility of using leptin and adiponectin to treat body fat irregularities in people with HIV; study results can be expected at future conferences.

Following the early success of protease-sparing regimens, some researchers are now exploring “nucleoside-sparing” regimens that omit NRTIs, the drugs most strongly associated with mitochondrial toxicity (damage to energy-producing organelles within cells). Studies at ICAAC showed that a regimen of lopinavir plus either efavirenz or saquinavir (Fortovase) without NRTIs had good antiretroviral potency.

Among the NRTIs, d4T is most clearly associated with numerous side effects including lipoatrophy (loss of body fat, especially in the face and limbs) and mitochondrial toxicity. Researchers reported that people who discontinued antiretroviral therapy due to hyperlactatemia (high lactic acid levels, a symptom of mitochondrial toxicity) could restart treatment with a regimen that contained AZT, 3TC, or abacavir (Ziagen)—NRTIs that are less likely to cause mitochondrial damage than d4T or ddI. Other studies showed that people who switched from d4T to abacavir, AZT, or tenofovir DF (TDF, Viread) regained some lost fat and showed less evidence of mitochondrial toxicity. Tenofovir is a newly approved nucleotide reverse transcriptase inhibitor (NtRTI) that so far has shown good efficacy and a favorable side effect profile.

For conference programs, abstracts, and additional coverage see:

XIV International AIDS Conference

www.aids2002.com

www.hivandhepatitis.com/2002conf/14th_aids/main.html

www.natap.org/2002/barcelona/ndxbarcelona.htm

Workshop on Adverse Drug Reactions and Lipodystrophy

www.hivandhepatitis.com/2002conf/adversedrug/main.html

www.natap.org/2002/lipoWorkshop/ndxLipo.htm

42nd ICAAC

www.icaac.org/42ICAAC.asp

www.hivandhepatitis.com/2002conf/iccac2002/main.html

www.natap.org/2002/ICAAC/ndxICAAC.htm

Priority Status for T-20

On October 11 the U.S. Food and Drug Administration (FDA) granted priority review status to the first fusion inhibitor, T-20 (known generically as enfuvirtide). T-20 works by preventing HIV from entering cells. The drug—to be marketed under the brand name Fuzeon—was jointly developed by Trimeris and Hoffmann-La Roche. The companies submitted an NDA for T-20 in September based on results presented at the Barcelona AIDS conference. The study showed that after 24 weeks T-20 reduced HIV viral loads and increased CD4 cell counts in heavily treatment-experienced people; 37% in one study and 28% in another achieved undetectable viral loads (below 100 copies/mL). Although T-20 is active against HIV that has developed resistance to other antiretroviral drugs, data presented at ICAAC indicate that it is most effective in individuals with less resistance. As reported in the June 2002 issue of *Antimicrobial Agents and Chemotherapy*, T-20 itself can lead to resistance when used alone, and Roche recommends that it be used as part of a combination regimen. While T-20 has a favorable side effect profile, it requires refrigeration and careful mixing and must be injected under the skin twice daily, which may make adherence difficult.

The FDA is expected to make a decision on T-20 by March 2003, and if the outcome is favorable the drug could be available shortly thereafter. Treatment advocates fear that because T-20 is difficult to manufacture, it will be more expensive than other anti-HIV drugs—possibly \$10,000–15,000 per year. Roche warned in August 2002 that supplies of the drug are limited, but said the company is working to increase production capacity.

New Rapid HIV Test Approved

On November 7 the FDA approved OraQuick, a long-awaited rapid HIV antibody test that provides results in about 20 minutes. To use the new test, a health-care worker takes a drop of blood using a finger stick (rather than drawing blood from a vein) and places it in a developing solution; the test strip changes color to indicate results. Although OraQuick is effective in ruling out HIV infection, if the results are positive a confirmatory test should be done.

Federal officials requested that manufacturer OraSure Technologies apply for a waiver to make the new test more widely available at small clinics and test sites that do not have certified laboratories. To receive the waiver, OraSure must conduct further testing to determine whether providers with less training can accurately administer the test and interpret results. With existing widely used antibody tests, people usually must return to a test site after 1–2 weeks to receive their results; about 50% never do

so. Advocates hope the new test will encourage more people to learn their HIV status and begin treatment earlier.

Two New Hepatitis Treatments Approved

The FDA recently approved two new treatments for viral hepatitis. On October 16 the agency approved Pegasys brand pegylated interferon-alpha-2a, manufactured by Hoffmann-La Roche, for the treatment of hepatitis C virus (HCV) infection. Pegylated interferon is a chemically altered form of interferon that lasts longer in the body and can be injected once rather than three times per week. Studies have shown that Pegasys in combination with the NRTI ribavirin is more effective than standard interferon plus ribavirin for both HIV/HCV-coinfected persons and those with HCV alone. In December the FDA approved combination therapy with Pegasys and Copegus, Roche's brand of ribavirin.

In September the FDA approved adefovir (Hepsera) for the treatment of hepatitis B virus (HBV) infection. Research indicates that adefovir is effective against HBV (including 3TC-resistant strains) in both HIV/HBV-coinfected people and those with HBV alone. Adefovir is active against both HBV and HIV. The drug (then called Preveon) was developed as an anti-HIV medication, but was never approved because it caused kidney toxicity; Hepsera is used in lower doses (about one-tenth as much) to treat hepatitis B and therefore is safer.

For more on treatment of viral hepatitis in people with HIV, see "HIV and Hepatitis Coinfection" on page 32.

NDA Accepted for Emtricitabine

In early November Triangle Pharmaceuticals announced that the FDA had accepted the company's NDA for emtricitabine (FTC, Coviracil), a new NRTI drug. Promising study results for the drug were presented at the September ICAAC (see conference coverage above). The drug may be approved and on the market by the middle of 2003. The company is also applying for approval in Europe.

Amprenavir Label Change

In August the FDA announced a change in product labeling for amprenavir (Agenerase). The new precautions concern use of amprenavir with methadone or oral contraceptives. According to the new label information, coadministration of amprenavir and methadone can lead to decreased blood levels of methadone and decreased plasma amprenavir concentrations. Lower methadone levels could result in opiate withdrawal symptoms, and methadone dosages may need to be increased. The label suggests that "alternative antiretroviral therapy should be considered" for people using methadone.

Regarding oral contraceptives, the new label advises that women taking amprenavir should not use hormonal contraceptives containing ethinyl estradiol and norethindrone because the pills can lead to decreased concentrations of amprenavir, potentially leading to loss of virological control. "Alternative methods of contraception are recommended" for women taking amprenavir, the label advises.

New Guidelines Recommend Longer Treatment Delays

New International AIDS Society-USA (IAS-USA) guidelines for HIV treatment published in the July 10, 2002 issue of the *Journal of the American Medical Association* and announced at the Barcelona AIDS conference suggest that asymptomatic people with HIV can safely wait longer before starting therapy. The panel recommended that treatment should begin when CD4 cell counts fall to between 200 and 350 cells/mm³. The current U.S. Department of Health and Human Services guidelines recommend treatment when CD4 cell counts fall below 350 cells/mm³, and earlier guidelines had set the level at 500 cells/mm³. Recommendations are tending toward later therapy in part due to a greater recognition of and concern about drug side effects and resistance. While HIV treatment may be beneficial for some people with higher CD4 cell counts, the authors said that for this population the risks of therapy generally outweigh the benefits.

Later initiation of treatment is supported by two studies presented in Barcelona. Alvaro Munoz, PhD, of Johns Hopkins University in Baltimore, Maryland, and colleagues compared people who had started HIV treatment with CD4 cell counts below 200 cells/mm³, between 201 and 350 cells/mm³, or between 351 and 500 cells/mm³. They found no significant differences in outcome between those who started therapy with 201–350 cells/mm³ and those who started with 351–500 cells/mm³. In contrast, those who started with CD4 cell counts below 200 cells/mm³ had greater HIV disease progression.

New Recommendations for Metabolic Complications

In November the IAS-USA issued the first guidelines concerning metabolic complications related to HIV infection and antiretroviral therapy. The new guidelines—which cover assessment and management of insulin resistance, abnormal lipid metabolism, abnormal body fat distribution, lactic acid disorders, and bone loss (osteopenia and osteoporosis)—were published in the November 1, 2002 issue of the *Journal of Acquired Immune Deficiency Syndromes*.

The 12-member IAS-USA panel that compiled the guidelines recommended that fasting glucose and blood lipid levels should be measured before initiating antiretroviral therapy or when a regimen is changed, then again after

3–6 months, then at least annually thereafter. Lactic acid should be measured in people taking NRTIs who show signs of elevated levels and in pregnant women. In terms of management, the panel recommended insulin-sensitizing drugs such as metformin (Glucophage) for insulin resistance, fibrate drugs for elevated triglyceride levels, and pravastatin or atorvastatin to reduce cholesterol levels. In addition, the guidelines suggest that PIs should be avoided if possible in people with preexisting diabetes, high blood fat levels, or cardiovascular risk factors. The panel made no recommendations regarding management of abnormal body fat distribution.

According to panel chair Morris Schambelan, MD, of San Francisco General Hospital, “These recommendations are important for clinicians because significant metabolic complications are affecting as many as half of all HIV-infected patients on antiretroviral regimens,” and “are causing some patients to delay initiating therapy and others to reconsider their use of these life-saving medications.” Like the federal HIV treatment guidelines, the new recommendations are a “work in progress” and will be modified as new information becomes available.

Structured Treatment Interruption

Researchers are increasingly interested in using structured (or strategic) treatment interruption (STI)—carefully monitored breaks in antiretroviral therapy—to help reduce drug side effects, overcome resistance, and possibly boost the immune system’s response to HIV.

Studies indicate that STI appears to work best in people with low HIV viral loads and relatively high CD4 cell counts. At ICAAC Elana Seminari from Pavia, Italy, and colleagues presented results from an STI study called FROG that used a one-month-on/one-month-off treatment schedule. At the beginning of the study the 62 participants randomized to try STI had viral loads below 50 copies/mL and CD4 cell counts above 300 cells/mm³.

In this study, nadir (lowest ever) CD4 cell counts appeared to be more important than CD4 cell counts at the time STI was initiated. Participants who had ever had a CD4 cell count below 200 cells/mm³ (many in this study had nadirs below 50 cells/mm³) were at risk of having their counts once again fall below 200 cells/mm³ during off-treatment months. When CD4 cell counts fall to this level, people are at greater risk for opportunistic illnesses (OIs). Participants in this study were restarted on antiretroviral therapy if their CD4 cell counts fell to dangerous levels, but those with the lowest nadir tended to have poor CD4 cell recovery after resuming treatment. The results of this study suggest that people who have ever had a CD4 cell count below 200 cells/mm³ may not be good candidates for STI.

Manuel Fernández-Guerrero and colleagues from Madrid, Spain, offered more promising results for people with higher CD4 cell counts. In this study, also presented at ICAAC, 49 participants who had started HAART with CD4

cell counts of 300–500 cells/mm³ were taken off therapy. At the time of treatment discontinuation the average CD4 cell count was about 750 cells/mm³ and the average viral load was approximately 700 copies/mL. After 16 months without HAART, the average CD4 cell count was about 500 cells/mm³ and the average viral load was 45,000 copies/mL—still within the safe range based on the latest federal treatment guidelines, which recommend antiretroviral therapy for people with fewer than 350 CD4 cells/mm³ and viral loads above 55,000 copies/mL. Participants were able to regain virological control when they restarted HAART. The authors concluded that for asymptomatic people with baseline CD4 cell counts greater than 350 cells/mm³ and low viral loads, STI is “a safe practice that may improve quality of life, avoid drug side effects, and save money.”

In an article published in the September 15, 2002 issue of the *Journal of Infectious Diseases*, Pablo Tebas, MD, of Washington University in St. Louis, Missouri, and colleagues similarly concluded that STI can be safe as long as CD4 cell counts remain above 200 cells/mm³. Because CD4 cell counts can drop rapidly in some people, however, frequent and careful monitoring is necessary.

Another potential benefit of STI is reduced drug resistance and a reversion of mutated HIV to more drug-susceptible wild-type strains. At the Barcelona AIDS conference Christine Katlama, MD, of Hôpital Pitié-Salpêtrière in Paris and colleagues reported on over 30 people with viral loads of at least 50,000 copies/mL and CD4 cell counts below 200 cells/mm³. The researchers found that after stopping HAART for eight weeks, more than one-half of the participants again became responsive to at least one class of antiretroviral drugs to which they had previously developed resistance. Viral load levels dropped ten-fold when the subjects resumed HAART. And in the October 2002 issue of the *Journal of Acquired Immune Deficiency Syndromes*, Walter Hauke, MD, from Erlangen, Germany, and colleagues reported on a case in which the amount of multidrug-resistant HIV was greatly reduced after a seven-month treatment interruption. The man was able to successfully reinstate therapy with previously used medications, leading the authors to conclude that STI may allow for drug “recycling.” A similar study from Spain, however, showed no such benefits from stopping drugs for eight weeks.

While STI may have certain benefits, improved immune response to HIV does not appear to be among them. In the October 7, 2002 online edition of the *Proceedings of the National Academy of Sciences*, Annette Oxenius, MD, from Zurich, Switzerland, and colleagues reported that supervised breaks from antiretroviral therapy did not affect levels of HIV-targeting CD8 cells and were “generally unable” to reduce the HIV viral load set-point (the level at which the immune system initially holds viral replication, without treatment, at the end of acute infection) in the 97 participants studied. In contrast with some small previous studies, the authors concluded that STI does not appear to “train” the immune system to keep HIV under control.

New Findings on Long-Term Nonprogressors

The existence of long-term nonprogressors (LTNPs)—people who remain asymptomatic without treatment long after they become infected with HIV—has puzzled scientists for years. LTNPs, who make up an estimated 1%–5% of people with HIV, generally maintain relatively intact immune function, high CD4 cell counts, and low viral loads, sometimes after having the virus for 20 years or more.

In 1986 Jay Levy, MD, of the University of California at San Francisco (UCSF) discovered that the CD8 cells of LTNPs produce a protective chemical, which he called CD8 antiviral factor, or CAF. Since then, researchers have been unable to pinpoint what exactly the factor is. In 1995 Robert Gallo, MD, now director of the Institute for Human Virology in Baltimore, identified a group of beta-chemokines (MIP-1a, MIP-1b, and RANTES) that appeared to block HIV replication; however, these proved ineffective against HIV strains that utilize CXCR4 rather than CCR5 coreceptors. This fall two research teams proposed new candidates as the elusive CAF.

David Ho, MD, of the Aaron Diamond AIDS Research Center in New York City and colleagues reported in the September 27, 2002 online issue of *Science*, and also at ICAAC, that they had uncovered a family of proteins—called alpha-defensins—that may protect cells from HIV infection. Alpha-defensins act as “natural antibiotics” and are produced by immune system white blood cells called neutrophils. Dr. Ho now suggests that the chemicals are also produced by CD8 cells and are active against viruses. Dr. Ho’s team cultured CD8 cells from three LTNPs. When they introduced CD4 cells and HIV into the cultures, the virus did not infect the CD4 cells. After the researchers added antibodies that inactivated the alpha-defensins, however, HIV easily infected the CD4 cells. The team also used new protein chip technology to identify alpha-defensins based on their weight.

On the heels of Dr. Ho, Mark Connors, MD, of the National Institute of Allergy and Infectious Diseases (NIAID) and colleagues reported in the October 7, 2002 online edition of *Nature Immunology* that when the CD8 cells of LTNPs are exposed to HIV-infected cells, they proliferate rapidly and produce large amounts of a protein called perforin that kills virus-infected cells. Dr. Connors’ team compared CD8 cells from 15 LTNPs and 25 progressors.

Many researchers remain skeptical about the recent findings. “This is not it,” said Dr. Levy of Dr. Ho’s discovery. Dr. Levy maintains that CAF—whatever it is—blocks replication of HIV after it infects cells rather than preventing infection in the first place. Dr. Gallo suggested that there are probably multiple protective mechanisms operating in different LTNPs. “There is no single answer,” he said. Ultimately, researchers hope the new findings might lead to the development of effective novel HIV vaccines or drugs.

But even if one or both of the newest candidates proves protective against HIV in larger studies, such a prospect is many years in the future.

Looking at long-term nonprogression from a different angle, Mary Carrington, MD, of the National Cancer Institute and colleagues reported in the July 22 online edition of *Nature Genetics* that they had uncovered a genetic pattern associated with slower progression to AIDS. The genetic pattern includes two genes, one of which codes for a receptor on the surface of natural killer cells and the other of which codes for an HLA protein on the surface of white blood cells and other tissues. HLA markers are individualized identifiers that help the immune system distinguish the body’s own cells from foreign invaders.

Dr. Carrington’s team analyzed the genetic blueprints of over 900 people with HIV and found that about 10% of European Americans carry the two protective genes; the gene pattern was less common among African Americans. People who carry both genes—but not either one by itself—were shown to experience slower HIV disease progression. Dr. Carrington speculated that when the specific HLA protein and receptor are both present, natural killer cells can more easily recognize and destroy HIV-infected cells, thus keeping the virus in check. She emphasized, however, that not everyone with the newly discovered gene pattern will experience slower HIV disease progression, and that others who do not possess the gene pattern are nevertheless LTNPs—validating Dr. Gallo’s contention that multiple factors are likely involved in delayed progression to AIDS.

HIV in Fat Cells

France Pietri-Rouxel, MD, of the Institut Cochin in Paris, and Jacques Leibowich of Hôpital Foch in Suresnes, France, reported at a meeting of the Institute for Human Virology in September that HIV can infect fat cells. In particular, the virus was found in the abnormal fat deposits of HIV positive people with lipodystrophy (unusual body fat distribution). Dr. Pietri-Rouxel conducts operations in which she removes accumulated abdominal fat and transplants it to fill out the sunken cheeks of people with lipoatrophy. Dr. Leibowich detected HIV genetic material in samples of fat he had requested from Dr. Pietri-Rouxel for an unrelated study. Dr. Pietri-Rouxel then sought and found HIV in the fat of seven of her patients who were taking HAART and had undetectable blood viral loads. The researchers next plan to look for HIV in the fat cells of people without lipodystrophy. HIV has long been known to infect immune cells, especially those that carry the CD4 and CCR5 cell surface receptors. As it turns out, fat cells also carry CCR5. Institute for Human Virology director Dr. Gallo said the finding might help explain why HIV is so difficult to eradicate. “That could be a major contributor to the reservoir,” he suggested. “It could also be the reason that some people with HIV lose fat.”

Male Sexual Dysfunction and HAART

As if bone disease, body fat irregularities, and an increased risk of heart attacks were not enough, two new studies show that HIV positive men taking antiretroviral drugs are also more likely to experience sexual dysfunction.

Amy Colson, MD, from Harvard Medical School in Boston and colleagues conducted a retrospective survey of the medical records of 254 HIV positive men receiving care from a large New England health maintenance organization (HMO) between 1993 and 1998. The results were reported in the May 2002 issue of the *Journal of Acquired Immune Deficiency Syndromes*. All of the men received antiretroviral regimens that included a PI at some point during this period: indinavir (62%), nelfinavir (46%), ritonavir (46%), or saquinavir (41%); in many cases more than one of these drugs were used concurrently. At least three-quarters also received NRTIs. Only 27% used NNRTIs. Eighty cases of either loss of libido or erectile dysfunction were found in a search of the men's records. The rate of sexual dysfunction was highest in those taking ritonavir, followed by indinavir, nelfinavir, and saquinavir. NRTIs and NNRTIs as a class were not associated with sexual problems.

On the whole, the men had advanced HIV disease—not surprising since the survey time frame included years before the advent of PIs in 1996. The men also had a variety of other conditions often associated with sexual dysfunction including depression (35%), high blood pressure (14%), alcoholism (12%), and diabetes (7%). There were no significant differences in testosterone levels between men with and without sexual difficulties. Given the general ill health of the men in the early years of the survey period, the researchers said they expected to see a decrease in sexual dysfunction as more effective treatment with PIs became available. However, the opposite trend was seen, supporting an association between PIs and increased sexual dysfunction.

Francis Lallemand of INSERM in Paris and colleagues reported results from a more recent prospective study in the June 2002 issue of the same journal. The researchers looked at 156 gay and bisexual men with HIV with a median age of just over 40 years. One hundred and eleven men reported some degree of sexual dysfunction since they began taking antiretroviral therapy. The rates were similar in men who had taken HAART regimens containing a PI for at least a month, those who had stopped treatment more than one month prior to the study, and those who had never taken a PI (71%, 73%, and 65%, respectively). Altogether, 89% reported reduced or absent libido, 86% reported erectile dysfunction, and 59% reported ejaculatory difficulties. Only 18% said they had experienced sexual dysfunction before they tested positive for HIV, and 32% said they had experienced sexual problems after becoming HIV positive but before starting antiretroviral therapy. While some previous studies have suggested that PIs may be associated with

sexual dysfunction, this study found no differences related to whether or not the men were taking regimens that included a PI.

“Given the increased life expectancy of HIV-infected patients since the advent of HAART, their sexuality should no longer be considered only in terms of prevention of transmission,” wrote the authors. “Sexual dysfunction in these patients should be specifically diagnosed and treated as in patients with other chronic diseases such as diabetes, hypertension, and depression.”

Fumagillin for Microsporidiosis

Jean-Michel Molina, MD, of Hôpital Pitié-Salpêtrière in Paris and colleagues reported in the June 20, 2002 issue of the *New England Journal of Medicine* that the fungal antibiotic fumagillin (Fumidil B) can effectively treat microsporidiosis caused by the parasite *Enterocytozoon bienewisi* in people with immune dysfunction. Microsporidiosis is an intestinal infection characterized by chronic diarrhea, malabsorption, and wasting. Fumagillin is the first therapy that effectively clears the parasite. Study participants included ten people with AIDS and two organ transplant recipients (transplant recipients are given drugs that suppress immune function in order to prevent organ rejection). One-half received fumagillin and one-half were given a placebo. After two weeks, all six taking fumagillin achieved *E. bienewisi* clearance, compared with none of those taking placebo; the placebo recipients were then switched to open-label fumagillin and they too all cleared the parasite. Three of those taking fumagillin developed bone marrow toxicity and low blood cell counts; two later relapsed.

Companies Heed Call for Nonoxynol-9 Discontinuation

Major manufacturers of sexual lubricants have responded to activist pressure to remove nonoxynol-9 (N-9) from their products. N-9 is a detergent that kills sperm and many microorganisms. Long used as a contraceptive, N-9 was added to several brands of lubricants and condoms in the mid-1980s in the hope that it would help prevent HIV transmission. But research has shown that N-9 can cause vaginal and anal irritation that may promote the spread of HIV and other sexually transmitted infections (STIs).

Studies found that female sex workers who frequently used N-9 had a higher risk of HIV infection. More recently, research showed that N-9 caused shedding of the sheets of protective epithelial cells that line the anus. Both the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have issued cautions about the rectal use of N-9. According to a WHO report, there is no evidence that N-9-lubricated condoms provide any additional protection against pregnancy or STIs

(although it is better to use a condom with N-9 than no condom at all). These study findings and warnings were not widely disseminated, however, and a recent survey showed that over 40% of gay men preferred lubricants containing N-9, believing they offered extra protection.

In September a coalition of scientists and health groups—including the San Francisco AIDS Foundation, the Global Campaign for Microbicides, the American Foundation for AIDS Research, the Gay and Lesbian Medical Association, the National Women's Health Network, and Planned Parenthood—issued a letter calling on manufacturers to stop adding N-9 to sexual lubricants and condoms. (The call did not include contraceptive products designed exclusively for vaginal use.) The letter, along with an investigative series in San Francisco's *Bay Area Reporter* newspaper, led several stores to agree to discontinue sales of products containing N-9 and led manufacturers to agree to stop adding the ingredient to their lubricants. However, some manufacturers continue to add N-9 to condoms. Advocates are concerned that N-9 on condoms could potentially increase the risk of HIV transmission if a condom breaks.

HAART Not Associated with Adverse Birth Outcomes

According to a report in the June 13, 2002 issue of the *New England Journal of Medicine*, use of antiretroviral therapy during pregnancy does not appear to increase the risk of stillbirth or premature birth. Ruth Tuomala, MD, of Brigham and Women's Hospital in Boston and colleagues looked at the pregnancy outcomes of 2,123 HIV positive women who received antiretroviral therapy in seven clinical trials and 1,143 women with HIV who did not receive treatment. The women gave birth between 1990 and 1998. Because much of the time frame of the study covered years before the advent of PIs, only about 6% received combination regimens that included a PI. Nineteen percent used combination regimens without a PI and 74% received monotherapy. The study was initiated by the National Institutes of Health after some earlier studies suggested that anti-HIV therapy might be associated with poor birth outcomes.

After controlling for factors such as CD4 cell count and alcohol, tobacco, or illegal drug use, the researchers found that rates of stillbirth, premature birth, low birth weight, and abnormal APGAR scores (a measure of newborn viability that includes pulse, skin color, and respiration) did not differ significantly between the women receiving antiretroviral therapy and those not on treatment. Sixteen percent of treated women and 17% of untreated women delivered prematurely, and 16% in both groups gave birth to low birth weight infants (less than 2,500 grams). Outcomes were comparable between the women who received monotherapy and those who received combination therapy, and between those who did and did not use PIs.

Seven women (5%) who received PIs delivered very low birth weight infants (less than 1,500 grams) compared with 34 women (2%) who received non-PI monotherapy and nine women (2%) who received combination therapy without a PI. This trend was not significant, and the number of women receiving PIs was small. The researchers suggested that women with the most advanced HIV disease were most likely to receive PIs when they first became available, and that severity of illness might help explain the difference.

Dr. Tuomala concluded, "Our data provide reassurance that the risks of adverse outcomes of pregnancy that are attributable to antiretroviral therapy are low and are likely to be outweighed by the recognized benefits of such therapy during pregnancy."

HIV Superinfection Documented

In news that has implications for prevention and vaccine development, different research groups have recently reported cases of HIV superinfection.

The first case was reported at the Barcelona AIDS conference by Bruce Walker, MD, of Massachusetts General Hospital in Boston. The Boston man was one of 14 undergoing experimental STI under Dr. Walker's supervision. The man began treatment soon after his initial infection with HIV, and was taken off therapy periodically in the hope of boosting his immune response to the virus. He was doing well after two rounds of on again/off again treatment, but then—soon after having unprotected sex—experienced a dramatic increase in HIV replication. Researchers genetically sequenced the man's virus and found a new strain of HIV that was 12% different from his initial strain. The man was restarted on antiretroviral therapy, but responded poorly and experienced a decline in his condition.

Two more cases of superinfection were reported in the August 1, 2002 issue of the *Journal of Virology*. These cases, reported by Artur Ramos of the CDC and colleagues, occurred in injection drug users in Thailand. In both cases the second infections were detected several weeks after the individuals had apparently developed good antiviral responses to their initial infections.

Another case was also reported at the Barcelona conference and published in the September 5, 2002 issue of the *New England Journal of Medicine*. Bernard Hirschel, MD, Stephanie Jost, and colleagues from the University of Geneva reported on a 38-year-old HIV positive man who contracted a second strain of HIV more than two years after his initial infection in 1998. As part of a study of early HIV treatment, after two years of successful therapy the man received an experimental immune-boosting vaccine and was taken off therapy. Soon thereafter, in April 2001—after having unprotected sex while on vacation in Brazil—the man experienced a steep increase in viral load, leading to the recognition of a second infection with a new strain of HIV. The new strain was one that is common in Brazil but

uncommon in Europe. The man resumed antiretroviral therapy and has responded well.

Researchers are concerned that the recent case reports suggest that developing a vaccine that stimulates an effective immune response to HIV may be even more difficult than previously assumed. Dr. Walker's case indicates that a person who apparently has developed a good natural immune response to HIV is still susceptible to reinfection, even with a similar strain. Dr. Hirschel's case—in which the man was infected with a distinct strain from a different part of the world—emphasizes the difficulty of developing a vaccine that will be effective worldwide. Said Dr. Hirschel, "It just shows how little we understand what's happening with HIV-related immunity."

Although superinfection remains rare, the new findings lend weight to safer sex messages for people with HIV. Some individuals have concluded that since they are already infected, they can safely have unprotected sex with other HIV positive people. But as Dr. Walker's case illustrates, superinfection can lead to HIV disease progression and poor response to antiretroviral therapy. "With sexual activity seemingly increasing among persons with HIV-1 infection," Dr. Walker wrote in an editorial accompanying Dr. Hirschel's findings, "this is a public health message that needs to be broadcast loud and clear."

Liz Highleyman (liz@black-rose.com) is a freelance medical writer and editor based in San Francisco.

San Francisco AIDS Foundation Bilingual Hotline

(English/Spanish)

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Toll-Free in California

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The Many Faces of Human Growth Hormone

The story of human growth hormone (hGH) is colorful by drug industry standards. HGH, also known as somatotropin, was first used to treat stunted growth in children. Later it was used in people with HIV disease to treat the gauntness of AIDS-related wasting and, more recently, the fat accumulations associated with lipodystrophy. HGH also may play a role in immune reconstitution. Outside the field of HIV, this very expensive therapy has multiple indications. Unapproved uses for hGH run the gamut from muscle enhancer to purported cure-all. Not surprisingly, the man-made hormone does not always perform as desired. Yet new research into how hGH may fit into the future of HIV disease management warrants another look at this unusual drug.

Bob Roehr

History

Growth hormone is a protein produced by the pituitary gland, a small peanut-shaped “master gland” located at the base of the brain. The pituitary gland not only controls physical growth, but also regulates other glands throughout the body that produce hormones such as testosterone and estrogen.

Scientists first began to learn the secrets of growth hormone by studying and treating children who did not grow normally. Researchers found that injecting ground-up pituitary glands taken from cadavers into the children led to their normal growth and development. The process was limited by

the supply of pituitary glands, and the procedure carried a risk of transmitting slowly developing viral infections such as Creutzfeldt-Jakob disease, a variant of which is popularly known as “mad cow disease.” Ongoing therapy required the harvesting and pooling of glands from large numbers of cadavers.

The solution was genetic engineering, which became a cornerstone for the creation of the modern biotechnology industry. For hGH, the process involves inserting a gene into laboratory cell lines to produce the desired protein, growing huge numbers of these cells, then purifying out the protein they produce for subsequent human use. The insertion of

genes into cells is known as recombinant gene technology. The first version of recombinant human growth hormone (sometimes called rhGH) was made by Genentech of South San Francisco, California, and approved for sale by the U.S. Food and Drug Administration (FDA) in October 1985. Today several companies produce and market recombinant hGH under different brand names (see sidebar on this page).

Recombinant technology solved the problems of disease transmission and availability, but not of cost. hGH is extremely expensive—from several thousand dollars per year for limited supplemental use, to about \$35,000 per year for a child who completely lacks the protein. The huge cost (and profit) of making the complex molecule has encouraged manufacturers to find other uses for hGH beyond the initial indication for children with stunted growth.

Pituitary tumors, chronic illness, side effects of therapy for other medical conditions, and processes associated with aging all can contribute to reduced pituitary function and decreased production of growth hormone. Expansion of the hGH market to treat such conditions was a natural outcome, and the FDA has approved label indications for new uses as manufacturers have submitted evidence of success from clinical trials.

At the same time, some proponents of hGH paint a dazzling but false portrait of the substance. Many sites on the Internet tout hGH as a panacea for everything from losing weight to halting the aging process. Some bodybuilders use growth hormone, often illegally, to rapidly increase muscle mass. Claims have proliferated though evidence to support them is scant. Growth hormone can be very beneficial for correcting a deficiency, but having too much of it does not necessarily bring added benefit—though it does increase the risk of side effects. Nevertheless, illicit use of hGH appears to be widespread.

AIDS Wasting

AIDS wasting syndrome (cachexia) is a condition associated with advanced HIV disease. It involves overall weight loss, but more importantly, the loss of lean body mass, or muscle, which sometimes may be replaced by fat. Weight loss results from a number of factors, alone or in combination, including lack of appetite, nausea, diarrhea, oral problems that make eating difficult, and problems related to intestinal absorption and use of nutrients. The condition was much more prevalent in the developed world before combination antiretroviral therapy became available.

A correct diagnosis and the proper intervention for each individual are as important in treating AIDS wasting as they are for any other medical problem. Early intervention is often most successful, and a variety of effective and relatively inexpensive tools (such as nutritional supplements, appetite stimulants, and exercise) can be used. hGH is not a universal remedy for treating AIDS wasting. While it can have a dramatically beneficial effect in some individuals (presumably those with a deficiency of natural hGH), the majority may see no benefit.

HGH by Other Names

hGH (somatropin) is produced by several companies and sold under a number of brand names. The main distinction between them is that they are produced in different types of cell lines and have been evaluated in clinical trials for different indications. The FDA allows a company to claim a label indication only if it has conducted trials for a specific condition with that version of hGH. Most physicians, however, believe that the different versions of hGH have the same biological effects. The most common brands of hGH sold in the U.S. are:

Genotropin and Genotropin MiniQuick
manufactured by Pharmacia (Pfizer)

Humatrope
manufactured by Eli Lilly and Company

Norditropin
manufactured by NovoNordisk

Nutropin and Nutropin AQ
manufactured by Genentech

Protropin
manufactured by Genentech

Saizen
manufactured by Serono

Serostim
manufactured by Serono

The current hGH regimen for AIDS wasting consists of a daily injection administered at bedtime to mimic the natural cycle of growth hormone release into the bloodstream. The dose is 4–6 mg, based upon body weight. hGH alone is likely to result in weight gain that is primarily fat, while adding a regimen of resistance exercise, such as weight training, can help build lean body mass. The average cost of hGH therapy for AIDS wasting is approximately \$250 per day. Due to pressure from AIDS activists, Serono Laboratories, which produces a version of hGH known as Serostim, capped the cost of their hGH at \$36,000 per calendar year for qualified individuals. The company provides the drug free of charge beyond this point.

Lipodystrophy

The term “lipodystrophy” is broadly applied to issues of body fat irregularities and metabolic abnormalities associated with HIV disease. It can include the wasting of fat from the face, arms, legs, and buttocks, as well as an increase in fat around the abdomen and on the upper back. Metabolic

In broad terms, management approaches to lipodystrophy tend to be dictated by 'fashion' and perhaps 'marketing' rather than fact or science."

Graeme Moyle, MD

abnormalities include increased blood lipid (fat) levels and insulin resistance (inability of cells to properly use insulin, leading to blood sugar imbalances). There is little agreement on a measurable definition of lipodystrophy, which impedes research into the condition.

Consensus appears to have emerged, however, around the idea that there are likely several different biological mechanisms and various factors at play, either alone or in combination. Some of the manifestations of lipodystrophy may be associated with HIV infection itself, others with specific anti-HIV drugs, and still others with the natural processes of aging. The picture is further complicated by individual genetic factors, body chemistry, and lifestyle choices.

Successful strategies to treat the various manifestations of the syndrome have not been identified. "In broad terms, management approaches to lipodystrophy tend to be dictated by 'fashion' and perhaps 'marketing' rather than fact or science," writes Graeme Moyle, MD, of London's Chelsea and Westminster Hospital in the most recent *Medscape* treatise on the subject. Researchers are gathering scientific data to investigate the use of hGH for some symptoms of lipodystrophy—however curious it may seem to reverse increases in abdominal fat, for instance, with a drug that can promote fat gains in people with wasting.

Donald Kotler, MD, of St. Luke's-Roosevelt Hospital in New York City is the principal investigator of the most sophisticated study of hGH and lipodystrophy yet conducted. The trial is known as STARS—Serostim in the Treatment of Adipose Redistribution Syndrome (ARS is another proposed term for lipodystrophy). In late September Dr. Kotler presented the most recent results from the study at the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Diego.

The multicenter STARS trial randomized 239 HIV positive subjects (13% female, 20% non-Caucasian) with an abnormal waist circumference or waist-to-hip ratio (waist circumference divided by hip circumference) to take 4 mg hGH daily, 4 mg hGH every other day, or placebo for 12 weeks. Participants then entered a second 12-week phase during which those who had received daily hGH were randomized to receive placebo (27 subjects) or hGH on alternate days (23 subjects); those who began taking hGH on alternate days continued to do so (48 subjects); and the initial placebo group went on to take 4 mg hGH daily (53

subjects). Everyone received hGH at some point during the 24-week trial, but no one received it on a daily basis for more than half the trial.

Principal measurements for the trial were the reduction of visceral adipose tissue (VAT, which is firm, internal abdominal fat, not the soft fat that lies just beneath the skin); levels of non-HDL (non-high-density lipoprotein) cholesterol; insulin resistance; lean body mass; and self-assessed quality of life and body image. Increased VAT, elevated non-HDL cholesterol, and insulin resistance are risk factors for cardiovascular disease. DEXA scanning technology was used to measure internal VAT. Mean (average) age at baseline was 45; mean body mass index (calculated as weight divided by height squared) was 27 kg/m². Average baseline VAT was 331 cm² in men and 249 cm² in women, which was significantly greater than in healthy control subjects of similar sex and age.

Dr. Kotler's group found that daily use of hGH was necessary to achieve a statistically significant reduction of visceral fat (at least at the 4 mg dose) in the 151 subjects who completed 24 weeks. Switching to alternate-day use after initial daily use was sufficient to keep internal fat from returning, but if hGH was stopped completely, the fat came back. At 24 weeks, people who received daily hGH then placebo showed a mean reduction in VAT of 22.4 cm²; those who stayed on alternate-day dosing for the full 24 weeks had a mean reduction of 19.7 cm²; those taking placebo followed by daily hGH lost a mean of 30.5 cm²; and subjects who began taking daily hGH and continued on an alternate-day regimen had a mean reduction of 30.9 cm² of VAT. DEXA scanning showed that these reductions were primarily in trunk fat, not in the limbs. For the four groups mentioned above, the VAT fat losses were 1.9, 3.0, 3.5, and 5.0 lbs, respectively. Loss of limb fat was 0.2, 0.4, 1.1, and 1.5 lbs, respectively, with an average loss of about 0.25 lbs per limb.

HGH reduced non-HDL cholesterol levels in all groups, with the decline ranging from 6.6% to 8.4%. The greatest benefit came with daily dosing followed by alternate-day maintenance dosing. Those who were later switched to placebo saw their non-HDL cholesterol levels start to climb again, though levels were still below baseline 12 weeks after stopping the hGH injections.

S **eron Laboratories' patient assistance program, which provides hGH for AIDS wasting for compassionate use and support above the \$36,000 annual cap, can be contacted at 888-628-6673.**

With regard to insulin resistance, the three arms of the trial that started on hGH showed an identical pattern of an increase in mean area under the curve (AUC) serum insulin through week 12, then a significant decline toward baseline by week 24. (AUC here refers to total insulin concentration over a period of time.) The arm that started on placebo showed no increase until hGH was initiated; this group was not tracked long enough to note a decline. However, AUC insulin levels tend to correlate poorly with true measures of insulin sensitivity.

Dr. Kotler concluded that the reduction of VAT, the decrease in total and non-HDL cholesterol levels, and the return of insulin levels to baseline by the end of the study suggest that hGH therapy could lead to a reduction of cardiovascular disease risk in this population. Nevertheless, it is important to remember that these results are from limited clinical trials. No version of hGH is approved by the FDA for treatment of lipodystrophy. While physicians have the flexibility to prescribe off-label (unapproved) use of hGH, health insurance providers most often will pay for only label-indicated uses of a drug, and few people can afford to pay for hGH out of their own pockets.

Thymic Function

New evidence suggests that hGH also may enhance immune system restoration and HIV-specific T cell responses. At the XIV International AIDS Conference in Barcelona, Spain, this past summer, researchers from Chelsea and Westminster Hospital presented data showing a direct effect of hGH on thymic function in a very small group of people with chronic HIV infection taking antiretroviral therapy. The thymus, a lymphoid organ located behind the upper breastbone, is the site of T cell maturation and differentiation—that is, where these white blood cells learn to recognize antigens (substances that stimulate an immune system response).

After 12 weeks of hGH administration (4 mg per day), 11 of 12 subjects in this study showed significant increases in naive CD4 and CD8 cell counts, indicating boosted thymic activity. Naive T cells are necessary for immune reconstitution, as memory T cells are programmed to target previously encountered antigens and do not respond to new pathogens introduced into the body (for example, those causing certain opportunistic illnesses, or OIs). In addition, HIV-specific memory CD4 and CD8 responses were significantly improved in at least nine of the 12 subjects after 12 weeks of hGH therapy. The memory CD4 response, however, was sustained only in those who continued taking daily hGH (instead of alternate-day or twice-weekly dosing) through week 24.

While these recent data are intriguing, much more study is needed. Even if it proves viable, clinical use of this potential new indication for hGH is likely years away.

Risks and Side Effects

Because hGH is a protein that would be destroyed in the stomach and intestines by digestive enzymes, it cannot be

Like sidewalk vendors selling \$20 Rolex watches, Internet sites offer cut-rate growth hormone prices that often are too good to be believed—and should not be.

taken as a pill and must be injected subcutaneously (under the skin).

HGH should not be taken by people with acute critical illness due to complications of open heart or abdominal surgery, multiple accidental trauma, or acute respiratory failure. HGH may stimulate the growth of active tumors and should not be used by people who have cancers that are not under control. HGH also may affect blood triglyceride levels and may increase the risk of developing diabetes in those who are already at risk, particularly people who are obese. Individuals taking insulin may need to have their doses adjusted. In spite of Dr. Kotler's findings, there may be increased cardiovascular risk with long-term hGH use, perhaps related to insulin resistance. Studies of growth hormone have not been conducted in pregnant women.

Up to 50% of all people experience mild to moderate musculoskeletal discomfort when starting hGH, and about 25% experience some fluid retention and swelling of the hands and feet. While both generally decrease as the body becomes accustomed to the drug, a significant number of people must stop taking hGH due to these side effects. Some people develop carpal tunnel syndrome (CTS, a condition characterized by numbness, pain, or tingling in the wrists or hands) while taking hGH; CTS typically resolves when the drug is discontinued. Other possible side effects include nausea, diarrhea, flu-like symptoms, and chest pain; only rarely are these severe enough to require discontinuation of treatment.

Dollars and Fraud

The high price tag and potential off-label and illegal uses of hGH appear to be strong incentives for criminal activity by corporations and individuals alike. Genentech illegally promoted off-label use of hGH in the first decade after it was approved. The FDA sued, and in 1994 the company agreed to pay a \$50 million fine for the violations.

In late 2001 Phoenix, Arizona, witnessed a complex web of false drug orders, a bungled hijacking, theft, arson, insurance fraud, and murder over a shipment of hGH. A wholesale value of about \$1 million and a street value three times that amount set these events in motion.

Counterfeiting of hGH is a growing problem. Like sidewalk vendors selling \$20 Rolex watches, Internet sites offer

cut-rate growth hormone prices that often are too good to be believed—and should not be. But counterfeit drugs can also enter the regular distribution chain, complete with knock-off packaging and bogus manufacturing lot numbers. In January and May 2001, and again in May 2002, Serono and the FDA warned about circulation of counterfeit Serostim distinguishable only by small variations in lot number and package design. Some of the counterfeits have little or none of the claimed active ingredient and they may contain dangerous impurities.

Serono—though apparently no other manufacturer of hGH—considers the problem so significant that it established the Serostim Secured Distribution Program. As of November 1, 2002, the distribution network has been restricted, and every single dose of Serostim has a number and is tracked directly to the patient. This helps to assure the quality of the drug. It also minimizes the likelihood of drugs being diverted and reduces the potential for reimbursement fraud.

Bob Roehr is a journalist and medical writer based in Washington, DC.

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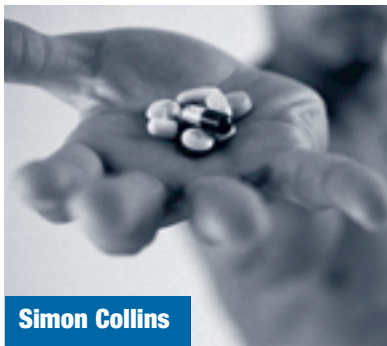
SALVAGE

Therapy

Salvage therapy is an approach taken when previous anti-HIV treatments fail to achieve desired goals, which include undetectable viral load, CD4 cell levels above 200 cells/mm³, and the prevention of HIV disease progression. It is one of the most difficult situations to face as a patient, and one of the most problematic challenges for health-care providers. Though sometimes euphemistically referred to as “management of treatment-experienced patients,” many HIV positive people, having already exhausted the benefits of at least a couple of drug combinations, think of their next regimen as salvage or “rescue” therapy.

A few physicians argue that due to cross-resistance among different drugs within the same class, people with HIV infection have only one good shot at treating it, and that any treatment regimen beyond the first is therefore salvage therapy. Others see salvage therapy as literally the end of the line—when an individual’s HIV has developed extensive resistance to all currently available treatments. But most providers consider salvage therapy to be somewhere in between these extremes. Understanding that the term can refer to different treatment situations is important.

Nevertheless, most of the information in this article will be relevant for anyone changing a drug regimen, no matter where that person is on the treatment path.



Simon Collins

Individualized Care

Salvage therapy is one of the most difficult topics to write about because every statement must be qualified in relation to an individual's personal treatment history. Although this should be the case with any medical decision, choices about HIV treatment should be tailored for each person. As therapeutic options become more limited, the stakes are arguably higher. More than at any other time in a person's treatment history, salvage therapy requires highly individualized care.

It is important for people to keep their own treatment history file that includes CD4 cell count, viral load, and resistance test results, together with a list of drugs previously used, medication allergies, past side effects, and adherence levels (frequency of taking doses as prescribed). As antiretroviral therapies become more effective, it is clear that we now need to plan for 30 years or more of treatment. Keeping complete treatment records is especially important when changing providers or hospitals.

Whether an individual has failed an initial regimen, has been HIV positive for many years and has used all the available drugs, or has been recently infected with a multidrug-resistant HIV strain, the approach will be similar. It involves looking at five or six key areas, each of which must be addressed to optimize the chances of success with a subsequent regimen. This highly individualized approach is not based on new science, and in fact has changed very little over the past three or four years.

Why Treatments Fail

Although the range of antiretroviral therapies has expanded, the basic principles of HIV treatment have been understood for some time and remain fairly constant. Apart from a few exceptions, such as recent research on viral fitness (replication capacity), most of the approaches discussed in this article are not new or recently discovered.

John Mellors, MD, of the University of Pittsburgh outlined the foundations of HIV therapy in a keynote speech opening the 1999 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Francisco. The multidisciplinary approach he described was also stressed at the Workshop on Management of Treatment Experienced Patients held in San Diego, California, this past September.

Both lectures emphasized that there are only a limited number of known reasons why treatment might fail: drug resistance, inadequate drug potency, suboptimal drug levels, poor adherence, and drug toxicity. At least

Reasons for Treatment Failure

- *drug resistance*
- *inadequate drug potency*
- *suboptimal drug levels*
- *poor adherence*
- *drug toxicity*

one—and possibly a combination—of these factors are responsible for the failure of each treatment regimen used in the past, whether it was the first or the fifth combination. To avoid repeating the same mistakes with salvage therapy, it is important to understand why each previous treatment attempt failed.

Resistance

Drug resistance is recognized as the reason most combination regimens fail, but how resistance develops is still often misunderstood.

The medical explanation for the development of resistance is that ongoing viral replication occurs in the presence of a drug regimen that does

not adequately suppress the virus. This means that if a person has a detectable viral load (over 50 copies/mL) while on treatment, enough new virus is produced each day for resistance to develop by chance due to random viral mutations (genetic changes). Once resistance develops by chance, however, if a person continues to take the drugs to which HIV is no longer susceptible, the resistant virus will continue to replicate until it becomes established as the majority strain.

Resistance, therefore, does not cause a treatment to fail, but rather develops if one or more of the other key factors related to treatment failure are present. If a combination regimen is not potent enough, if drugs are poorly absorbed, if adherence is not perfect, or if the drugs are not effective due to pre-existing resistance, a person may not achieve or maintain a viral load under 50 copies/mL. Then, as a result of continuing treatment with a detectable viral load, viral mutations may develop and resistance can follow.

However, studies show that if viral load is reduced to an undetectable level (usually below 50 or 25 copies/mL, depending on the assay) and all other factors related to treatment success are taken into account, then a combination regimen will continue to work and the virus is much less likely to develop further resistance. Individuals who achieve and maintain undetectable viral load levels with any drug combination, first-line or salvage, are in the best position to see their viral load remain this low for many years. The magnitude of the drop in viral load—even if it is reduced by hundreds of thousands of copies—is not as important as getting viral load as low as possible. Some studies suggest that it may be beneficial to aim for a viral load below 5 copies/mL; ongoing research should clarify whether this is important for long-term health.

Another important concept is that resistance rarely acts like an on-off switch. Think of resistance more as being on a continuum, with completely sensitive or even hypersensitive virus at one end and completely resistant

Considerations When Changing Antiretroviral Therapy

If viral load starts to rise above 50 copies/mL, don't panic—but do take it seriously.

- *Have a new viral load test done on the same day you get the results of the first test to determine whether the first result was accurate. Viral load levels often fluctuate, and a single high result may not indicate that treatment is failing. Collect the new test results as soon as they are available (usually within two weeks).*
- *Find out why the current drug combination failed. Was it due to resistance, lack of potency, poor adherence, suboptimal drug absorption, or a combination of these factors?*
- *Choose the most potent combination available for salvage treatment. Dose reductions or drug substitutions can always be considered later.*
- *Use as many drugs as possible that are not cross-resistant to previously used drugs. Ask for genotypic and phenotypic drug resistance tests.*
- *Monitor the effectiveness of the new regimen carefully, preferably with a viral load test 4–12 weeks after the treatment change, then every three months. Discuss any problems with adherence or side effects with a health-care provider.*
- *Find out what new treatments will become available and when, including through expanded access programs or clinical trials. Taking new drugs may not be necessary, however. If your CD4 cell count is stable, it may be better to save new drugs until they are most needed.*
- *Keep up to date on the latest research areas such as mega-HAART, structured treatment interruption, and new drugs in development.*
- *Even if viral load is detectable and new treatments are not available, staying on a regimen that partially suppresses HIV is much safer than stopping all drugs.*

virus at the other. In between these two extremes, other factors come into play. For example, HIV generally slowly accumulates mutations that gradually limit how effective protease inhibitors (PIs) are against the virus. But even with extensive resistance, the drugs still can have some clinical benefit. If a person with drug-resistant HIV discontinues treatment and viral load increases further, this is evidence that the drugs were providing some

anti-HIV activity. Since resistance is on a continuum, increasing the dose or concentration of a drug often can overcome resistance—although doing so may also increase drug toxicity.

Resistance Testing

Resistance tests are used to identify drugs that are not effective against an individual's specific strains of HIV. There are two main types of resistance tests. Genotypic tests look for genetic

changes in a person's virus and match these mutations against a database of known mutations that in clinical trials have been associated with resistance to different drugs. Phenotypic tests look at how viral replication is affected when increasing concentrations of different drugs are added to an individual's HIV in a test tube. A third variation called a "virtual phenotype" compares genotypic results with a large database of phenotypic results.

Both genotypic and phenotypic tests only detect resistance once it is relatively extensive. The tests are less sensitive to minority drug-resistant strains of HIV that are present in the body at low levels. For the most reliable results, the viral load should be above 1,000 copies/mL and the individual should currently be taking anti-HIV therapy. While several studies have shown that resistance tests can help physicians select an optimal drug regimen, other studies have not shown a dramatic benefit in terms of clinical outcome. This is likely because as a person's HIV becomes more resistant, there are fewer effective treatment options available. Resistance tests can tell which drugs are no longer active, but someone whose virus is no longer sensitive to any drugs will not be able to construct an effectively suppressive regimen.

Experts have begun to recognize the value of resistance tests at every important change in a person's HIV disease progression. Julio Montaner, MD, of the University of British Columbia in Vancouver has referred to the combined history of all of an individual's worst resistance profiles over time as "virtual resistance." Compiling such a profile involves blood tests when HIV is originally diagnosed and before starting treatment, a complete history of all drugs a person has taken, and viral load test results for the periods during which those drugs were used. It also requires knowing the exact timing of previous resistance tests and what drugs were being taken at the time of these tests.

Short-term treatment benefit has been observed when resistance testing is used in conjunction with therapeutic drug monitoring (TDM) to ensure optimal drug levels (discussed below). Long-term TDM data for anti-HIV medications are not yet available.

Drug Potency

Potency refers to the strength of drugs in a combination regimen—how effective they are at reducing viral replication and maintaining a response. On a basic level, drug potency refers to

how much of a viral load reduction a drug generates by itself. The greater the potency of each drug in a combination, the greater the magnitude and durability of viral load reduction.

Anti-HIV drugs are approved only when they show a clear antiretroviral effect; even the newest drugs that have been studied for use in salvage therapy must show this effect. For example, results from a recent study of the fusion inhibitor T-20 (enfuvirtide, Fuzeon) showed that T-20 added to the best available existing choice of therapy produced a 1.7 log reduction in viral load, while the best existing regimen alone produced only a 0.7 log reduction. The European/Australian segment of this study (TORO 2) showed slightly less of an effect (1.4 log and 0.6 log reductions with and without T-20, respectively) in people who had more resistance to existing

2.5 logs. Therefore, at least three highly suppressive drugs are generally required to reduce viral load from baseline to an undetectable level. By definition, people who require salvage therapy do not have three potent drugs available, so regimens with larger numbers of drugs—sometimes up to nine—may be needed to achieve adequate potency. Even drugs that are not very potent by themselves can still contribute some antiretroviral activity to a combination.

Potency depends not only on the effectiveness of a drug itself and the other drugs it is used with, but also on the specific virus it is used against. A few drugs can be more effective against drug-resistant virus than against wild-type (nonmutated) HIV, but in general, resistance and previous treatment experience render new drugs less potent. For example, studies have

Even drugs that are not very potent by themselves can still contribute antiretroviral activity to a combination.

drugs before they started the study. From this, it appears that T-20 can produce an approximate 1 log reduction in viral load, although this will of course vary among individuals.

The reason combination antiretroviral therapy includes three or more drugs is largely linked to the issue of potency. The potency of a regimen is determined not only by the activity of each drug, but also by the combined activity of the regimen as a whole. The overall potency of a combination regimen must be strong enough to reduce viral load from baseline to an undetectable level and to maintain this response for months and, ideally, years.

If a single drug could produce a 5 log or 6 log reduction in viral load on its own, it could theoretically be used without other drugs in a combination (although resistance is more likely when a drug is used alone). However, existing drugs produce viral load reductions only of about 0.4 to about

shown that the recently approved nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir DF (TDF, Viread) produces an average 0.6 log viral load reduction in treatment-experienced people compared with a 1.1 log drop in those who are treatment-naive. Tenofovir may therefore contribute more potency as part of a first-line regimen than as part of a salvage regimen.

Suboptimal Drug Levels

A third important reason for treatment failure is suboptimal drug levels in the body. Suboptimal drug levels may be due to inadequate dosing, but may also be related to individual differences in pharmacokinetics (drug absorption, metabolism, and excretion). How drugs are absorbed in the body is highly individual, and blood drug levels are subject to significant variation among different people taking exactly the same dose. For some drugs used for conditions other than HIV this

People who metabolize drugs faster than average run the risk of developing resistance due to suboptimal drug levels. Those who metabolize drugs more slowly than average may experience increased side effects due to high drug levels.

is not a problem, because their generally low toxicity means the drugs can be given in sufficiently high doses to allow for this variability. But this is not the case for most anti-HIV medications. Due to the toxicity of antiretroviral drugs, the highest tolerable dose may be only just above the minimum dose required to avoid resistance.

Many antiretroviral drugs are metabolized in the liver by the cytochrome P450 (CYP450) enzyme system. Some people naturally metabolize drugs more slowly or more rapidly than others. For example, those with existing liver damage often have impaired drug metabolism. People who metabolize drugs faster than average run the risk of developing resistance due to suboptimal drug levels. Those who metabolize drugs more slowly than average may experience increased side effects due to high drug levels. Among people who metabolize drugs quickly or do not achieve adequate concentrations in the body for other pharmacokinetic reasons, even perfect adherence will not ensure safe levels.

In addition, drugs that are metabolized by the CYP450 pathway can interact. When multiple drugs that use the same pathway are present, metabolism may be slowed, leading to higher drug levels. In other cases, certain drugs can stimulate CYP450 metabolism, leading to more rapid drug processing and lower levels. Every recent medical conference on AIDS has included reports about drug interactions, often involving medications that have been licensed for many years. Some foods and herbal remedies (for example, grapefruit juice and St. John's wort) can also affect drug metabolism.

Peak and trough levels and area under the curve (AUC) are important

concepts in understanding drug levels. The peak level is the highest drug level in the body after taking a dose. The trough level is the lowest drug level between doses, usually reached right before the next scheduled dose is taken. On a graph, the line that joins the peak and trough levels is a curve; therefore, the amount of drug exposure over a dosing interval is represented by the "area under the peak/trough curve," or AUC.

It is best to have a constant therapeutic drug level in the body over time, since high levels can cause increased side effects and low levels can promote resistance. Several new antiretroviral drug formulations are designed to last longer in the body and achieve steady drug levels with a single daily dose.

Sometimes low drug levels and resulting drug resistance can be overcome with higher doses. Increasing drug dosages can produce a stronger antiviral effect, but also heighten the risk of side effects. For example, it is well known that the first studies of AZT (zidovudine, Retrovir)—which used three or four times the current accepted dose—led to side effects that were very difficult to tolerate. What is less well known is that AZT monotherapy at these high doses produced about a 4 log reduction in viral load. Using such high doses as part of salvage therapy is not common, but may be useful on an individual basis (though only in consultation with a physician).

With regard to T-20, it should be noted that maximum dose cut-offs for efficacy or tolerability were not reached in the registrational studies due to supply problems and the difficulty of asking subjects to inject the drug more than twice per day. There may therefore

be a subgroup of people using T-20 in the context of salvage therapy who could benefit from the potentially greater antiviral activity of higher doses.

Drug Boosting

One way to increase the antiretroviral activity of a drug is to add another medication that "boosts" the blood level of the first drug. As discussed above, this works because certain medications inhibit drug metabolism in the liver.

Ritonavir (Norvir) is used most often to boost the levels of other PIs. Numerous studies have shown that using ritonavir to boost indinavir (Crixivan) can overcome indinavir resistance; however, as blood levels of indinavir increase, so too does the incidence of side effects. The new PI Kaletra includes a small amount of ritonavir in the pill to increase levels of lopinavir. The added ritonavir boosts lopinavir well above the minimum concentration needed to inhibit 50% or 95% of viral replication (called the IC_{50} or IC_{95} , respectively; IC refers to the "inhibitory concentration" as determined in laboratory tests). This is one of the reasons Kaletra has proven to be so effective against HIV that is resistant to older PIs. Lopinavir itself has a resistance profile similar to that of other PIs, but boosting with ritonavir can overcome this resistance.

As another example, a recent study suggested that using a low dose (300 mg) of hydroxyurea (Hydrea) twice daily could enhance the activity of ddI (didanosine, Videx) while reducing ddI toxicity. It has also been suggested that mycophenolate (mycophenolic acid, CellCept; used in organ transplantation) can similarly increase the potency of abacavir (Ziagen) and a few other nucleoside reverse transcriptase inhibitor (NRTI) drugs, although clinical benefit from this approach has not been clearly shown in recent studies.

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) refers to measuring the levels of medications in the body. The goal of TDM is to help achieve optimal drug levels on an individualized basis. The technique can provide protection against

excessively low or high drug levels, and thereby improve virological outcomes and reduce toxicity. TDM is most useful with PIs and may also be used with non-nucleoside reverse transcriptase inhibitors (NNRTIs); however, it is not recommended for NRTIs due to current technological limitations. Results from a large European trial (named ATHENA) of subjects taking their first antiretroviral regimen showed that TDM led to lower rates of treatment discontinuation and higher rates of virological response. Some clinicians believe TDM may be beneficial for people taking salvage regimens as well.

By helping to optimize treatment, TDM can lead to the use of very different dosing regimens in different individuals. For example, indinavir/ritonavir is often dosed at 400 mg/100 mg twice daily in France, where TDM is widely used. (The typical dose in the U.S. is 800 mg indinavir with 100 or 200 mg ritonavir twice daily.) People in the Netherlands using the original formulation of saquinavir (Invirase) with the benefit of TDM received “double dosing” and avoided the early failures seen in the U.S. due to suboptimal drug levels. And in the UK, a patient whose damaged liver allowed only extremely slow metabolism of efavirenz (Sustiva) was given a low dose of 200 mg twice weekly prior to a liver transplant.

Such individualized dosing is possible only when drug levels can be monitored and adjusted on a person-by-person basis; it is not possible simply to guess drug levels. Further research needs to be done in this area, however, as optimal drug levels are not precisely understood and drug level tests have not been standardized.

Scientific opinions about TDM differ considerably between Europe and the U.S., as does access to it. Countries in Europe with leading research programs on drug metabolism already have laboratories that can analyze blood drug levels in people receiving antiretroviral therapy. In the Netherlands TDM is part of the standard of care; all people starting anti-HIV regimens that

include a PI or an NNRTI have their levels of these drugs measured. In France TDM is not universal, but it is widely used, especially for people receiving salvage therapy. In the UK TDM is available to a wide range of people, mainly those using PIs. Use varies by clinic, and some offer TDM to all patients; due to the efforts of treatment advocates in the UK, the additional cost of the tests is covered by drug manufacturers.

Availability of TDM in the U.S. has increased over the past few years, although it is still uncommon. U.S. clinicians generally are ambivalent about the benefits of TDM for anti-HIV therapy due to the wide variability of drug levels within a single individual (especially due to timing of doses, food requirements, and varying adherence levels over time), uncertain therapeutic ranges of anti-HIV medications, lack of standardization of drug level measurements, variability in laboratory accuracy, and difficulties in interpreting TDM results. Some providers also question the value of measuring boosted PI combinations (that is, regimens with minimized peak/trough variability).

Yet clinicians such as Steve Miles, MD, of the University of California at Los Angeles (UCLA) nevertheless believe that TDM can help individualize HIV treatment, including in people whose previous regimens have failed and in those with few therapeutic options, for whom “a mistake in drug levels could doom a regimen.” (Dr. Miles also noted that TDM is reim-

acknowledging difficulties in this rapidly changing area of treatment, the committee also provided guidelines to assist clinicians, particularly when using TDM in conjunction with phenotypic testing for people receiving salvage therapy. Encouragingly, Edward Acosta, PharmD, from the AACTG committee, in a lecture on TDM use in the U.S. at the September 2002 ICAAC, concluded that “TDM will likely be incorporated into treatment, especially in salvage therapy...and especially if the rate of new drug development is unable to keep pace with the development of resistance.” (See also “Therapeutic Drug Monitoring,” *BETA*, Autumn 2000, page 22. For information on a currently enrolling trial studying TDM, see page 47 in this issue.)

Combining TDM and Resistance Testing

While the benefits of resistance testing and TDM on clinical outcome have been evaluated separately, two important resistance studies showed that both drug sensitivity and optimal drug levels are necessary to achieve a sustained virological benefit from treatment.

In the GART study, Douglas Mayers, MD, of Henry Ford Hospital in Detroit, Michigan, and colleagues studied 153 subjects who experienced a greater than three-fold rise in HIV viral load while using a regimen containing a PI and two NRTIs for over 16 weeks. Subjects were randomized to receive either treatment recommendations

Both drug sensitivity and optimal drug levels are necessary to achieve a sustained virological benefit from treatment.

bursed by Medicare and Medi-Cal at approximately \$40 per assay.)

In a position paper published in the August 10, 2002 issue of *AIDS Research and Human Retroviruses*, the Adult Pharmacology Committee of the U.S. Adult AIDS Clinical Trials Group (AACTG) stated that “data generally support the use of TDM.” While

based on genotypic testing or else no genotypic test results. In a pharmacokinetic substudy, blood levels of all drugs (including NRTIs) from random (untimed) samples from 147 participants were measured using the VircoPK assay at baseline and at weeks 4, 8, and 12. The week 12 results were used to determine whether individual subjects

had drug levels above or below the median. Genotypic and phenotypic test results were also used to determine the number of more active and less active drugs for each participant. Researchers calculated viral load changes from baseline to week 12 and their relation to drug levels. Inhibitory quotients (IQs, see sidebar on this page) were calculated as drug level at week 12 divided by fold change of IC_{50} at baseline, and were also classified as being above or below the median for the group.

Suboptimal levels of more active drugs led to a reduced antiviral effect compared with higher concentrations of less active drugs, reaching statistical significance for the genotypic analysis. A clear relationship was also found between the average change in viral load at week 12 and the number of drugs with mean IQ above the group median. For the cohort as a whole, the additional viral load reduction was 0.2 logs for each drug with an IQ above the median. Even though the differences in this study may appear small, they can be significant in a salvage setting in which any added viral suppression is likely to contribute to a longer duration of response to treatment.

The VIRADAPT study showed a virological benefit when using genotypic resistance test results to guide treatment choices for second-line and salvage therapy combinations. Results were presented by Rodolphe Garraffo, PharmD, and colleagues from Nice, France, at the September 1999 ICAAC and published in the July 7, 2000 issue of *AIDS*. Drug level monitoring for PIs was also done in this study to determine the impact of medication levels on therapeutic success or failure.

Eighty-five participants (49 in the genotypic testing arm and 36 in the control arm) received 575 PI drug level measurements. Participants were considered to have optimal drug concentrations if two or more measurements were greater than the IC_{50} for the specific PI they were receiving. Subjects who had two or more measurements below the IC_{50} were considered to have suboptimal drug concentrations. Participants with suboptimal drug concentrations achieved a 0.3 log

reduction in viral load at week 48, compared with a 1.2 log decrease in those with optimal drug concentrations. In a multivariate analysis, drug concentrations above the IC_{50} , the use of genotypic testing, and the presence of primary resistance mutations for PIs were independently associated with virological response.

Adherence

Some providers believe that adherence is often the likeliest cause of

treatment failure; drugs cannot be effective if people are unable to take them as prescribed. As discussed above, due to toxicity the highest tolerable dose of an antiretroviral drug may be only just above the amount needed to avoid resistance. Missing even an occasional dose can cause drug levels between doses to fall so low that the drug no longer suppresses the virus. This is a particular concern with once-daily medications, since more time passes between doses and the virus

The inhibitory quotient (IQ) is a measure of drug exposure and susceptibility in an individual. It is typically calculated as the minimum drug concentration (C_{min}) divided by viral susceptibility to that drug in an individual (IC_{50} or fold change as measured by a phenotypic assay). In the case of virtual phenotyping, the virtual IC_{50} (the fold change reported in this test) is used and the IQ is referred to as the virtual inhibitory quotient (VIQ).

The IQ or VIQ may prove to be a more practical measure of resistance than genotyping or phenotyping alone because it combines drug susceptibility and drug exposure. Several studies have shown that increasing drug doses can sometimes overcome reduced susceptibility. By relating individual drug exposure to the level of viral resistance in that same person, a more accurate prediction of virological response to that drug may be achieved.

For example, a person may have perfect adherence—allowing adequate drug levels—but moderately resistant virus, and therefore therapy may fail despite the good drug levels. The IQ or VIQ provides additional information along with phenotypic testing and therapeutic drug monitoring, and serves as a guide for dosage adjustment in order to achieve the drug levels needed to overcome resistant virus.

Although IQ and VIQ measurements are a relatively new concept, their integration into clinical care for salvage therapy could provide another opportunity for individualization. Yet until these measurements are standardized to define therapeutic and toxic IQ levels, their use in clinical practice will remain limited.

Viral FITNESS

Viral fitness refers to HIV's ability to replicate and infect new cells. Strains of HIV often become less fit and presumably less harmful as they mutate to resist drugs; nonmutated virus is known as wild-type virus.

Researchers from the Royal Free Centre for HIV Medicine in London have developed a model for rotating drugs as monotherapy, dual therapy, or triple therapy on a daily or weekly basis. Using a model allowing for 128 different subpopulations of virus and combinations of seven anti-HIV drugs, Andrew Phillips, PhD, and colleagues calculated that sequential daily or weekly monotherapy with the seven different drugs was as likely to produce sustained 3 log viral load reductions over three years as continuous use of a seven-drug combination regimen. According to the model, in some circumstances dual or triple therapy may be more likely to work than monotherapy, and it would probably be best to start with such combinations. The only advantages of monotherapy are reduced toxicity and cost.

Although viral resistance would be present on each day of treatment, the sequential regimen would remain effective because any given subpopulation would not have time to grow sufficiently during the short period in which a specific drug was used. One caution with this approach is that it may require more classes of drugs than are currently available. However, if the rationale is plausible, this strategy would work best for people who have already developed the most resistance, who arguably have

therefore has more time to replicate in the absence of an adequate concentration of the drug in the event of a missed dose. Following the dietary requirements for a medication is also important.

While some people can be 100% adherent and still experience treatment failure due to pre-existing resistance, suboptimal drug levels, or an insufficiently potent regimen, many others will not have been as adherent as they wanted or needed to be.

Adherence rates among people taking anti-HIV therapy are probably higher than for practically any other condition—including other life-threatening infections—yet even this high adherence rate is not high enough. Although the importance of adherence may be widely recognized, it remains problematic in day-to-day practice. For many people, the need for salvage therapy may provide an opportunity to take treatment more seriously than ever before.

If adherence has been very poor, a person may have avoided resistance because of insufficient continuous drug levels. That is, the concentration of a medication may have been too low to pressure the virus to develop drug-resistant mutations. This possibility should be taken seriously. Before choosing new drugs, people who are considering changing their treatment regimens due to viral load rebound should tell their health-care providers how they were actually taking their medications. Resistance testing may be another way to confirm whether drug resistance has developed.

Getting adherence right should be the primary focus for people on any therapy until they develop good habits. Support programs and adherence teams (i.e., peer advocates, social workers, pharmacists, and nurses) can be more helpful than many doctors, and often are more trusted by patients. These adherence experts can provide tips and tools such as timers, phone reminders, and beeping pillboxes. Support for adherence should be included as part of every treatment plan. Designing a strategy for near-perfect adherence when taking salvage

therapy can be as beneficial as having access to a new drug.

Drug Toxicity

Drug toxicity leading to discontinuation is another possible cause of treatment failure. For a minority of people, severe or life-threatening reactions to anti-HIV medications can eliminate these drugs as options, and therefore can be seen as medically responsible for treatment failure. Hypersensitivity reactions to abacavir and nevirapine (Viramune), hepatotoxicity (liver toxicity), seriously elevated lipid levels, and manifestations of mitochondrial toxicity (for example, muscle aches and weakness) can all lead to drug discontinuation.

Less serious toxicities may also lead to treatment failure if they are not managed properly. For example, diarrhea and vomiting can prevent adequate drug absorption. Any side effects that have a negative impact on quality of life may lead to problems with adherence. Close monitoring and effective management of side effects can only increase the chances of successful treatment. In some cases, switching drugs to improve tolerability may also be important.

A session at the Workshop on Management of Treatment-Experienced Patients this past September highlighted the importance of drawing upon specialized expertise to prevent and manage both side effects and opportunistic illnesses (OIs). This may become increasingly important in the case of side effects that are outside the realm of expertise of most clinicians trained in infectious disease management, such as elevated blood lipid levels and loss of bone mineral density.

Salvage Therapy Strategies

Addressing the various factors that contribute to treatment failure can improve the likelihood of successful salvage therapy. Two management approaches will be discussed below: whether or not to interrupt therapy before starting a new salvage regimen,

and whether there is a benefit to using multiple drugs in salvage therapy. Both approaches have been used in salvage therapy settings in well-publicized cohort studies from London, Frankfurt, Montreal, and Paris. They are being further studied in a large, randomized international trial called OPTIMA. (The future of this study is currently unclear due to slow enrollment; many researchers and participants are reluctant to accept randomization in the context of salvage therapy.) For more information about OPTIMA and other salvage therapy trials, see page 46.

To Interrupt or Not to Interrupt?

There are several reasons underlying the strategy of interrupting therapy before starting a new salvage regimen. These include allowing a reversion from resistant to wild-type virus, a break from side effects, and a short period to psychologically prepare to cope with a subsequent mega-HAART combination (a regimen containing five or more drugs).

The French GIGHAART study showed that a treatment break of eight weeks prior to optimized salvage therapy could dramatically increase the chances of subsequently achieving virological benefit. Results were presented by Christine Katlama, MD, of Hôpital Pitié-Salpêtrière in Paris and colleagues at the 8th European Conference on Clinical Aspects and Treatment of HIV Infection in October 2001, and again at more recent conferences. In this randomized study, the arm that took a break before resuming treatment and the arm that immediately started salvage therapy both experienced a viral load decrease greater than 1 log over the first two weeks. However, viral load gradually rebounded in the immediate treatment arm, leaving only a 0.4 log drop from baseline at week 12. The deferred treatment arm experienced continued viral load decline to 1.9 logs below baseline. The greater benefit seen in the deferred therapy arm led to the early termination of the study.

Taking these results back to individualized care, the prospect of better

results with deferred therapy is exciting, but the potential risks are also very real. Treatment-experienced people who interrupt therapy will need more frequent monitoring and possibly prophylaxis drugs to protect them from developing OIs if their CD4 cell counts are at risk for dropping below 200 or even 100 cells/mm³. However, the cost savings from not using antiretroviral drugs during this period should easily cover the expense of additional monitoring.

Other studies of treatment interruption have shown that a CD4 cell decrease of more than 100 cells/mm³ may be expected, and that the optimum time to defer therapy appears to be 8–12 weeks. These results are from averaged data and, as always, treatment decisions should be individualized. Some people may need to start salvage therapy earlier, while others may be able to delay resuming treatment for longer periods.

Mega-HAART

The second main salvage therapy strategy is to increase the number of drugs in an antiretroviral regimen. Some studies have used combinations of up to nine drugs. Such studies looked at multidisciplinary approaches to salvage therapy in people who had run out of other treatment options and were happy to try a new strategy. Participants in the French GIGHAART study, for example, had CD4 cell counts under 200 cells/mm³, resistance to three classes of antiretroviral drugs, and a median viral load of over 50,000 copies/mL. It is notable that major studies of mega-HAART have used TDM to confirm the levels of each PI and NNRTI, and have adjusted doses appropriately on an individualized basis.

Combinations used in the GIGHAART study included three to five NRTIs (ddI, d4T [stavudine, Zerit], AZT, 3TC [lamivudine, Epivir], and/or abacavir) plus one NNRTI (nevirapine, delavirdine [Rescriptor], or efavirenz) plus three PIs (either 400 mg ritonavir/600 mg amprenavir [Agenerase] twice daily or 300 mg ritonavir/400 mg lopinavir twice daily, plus either 400 mg

few other alternatives and who therefore would be most likely to want to try this option.

At the 2002 International AIDS conference in Barcelona, Franco Maggiolo, MD, of Ospedali Riuniti in Bergamo, Italy, and colleagues presented very interesting results from a pilot study of a similar approach: cycling drug combinations to allow for constant selective pressure on the virus. They reported continued low levels of viral replication in a group of 34 subjects with HIV resistant to three drug classes; baseline viral load was about 25,000 copies/mL. Anti-HIV drug combinations were selected on the basis of genotypic resistance test results; no regimen included more than four drugs. Viral load was monitored every two months, and treatment was changed if viral load rose above 10,000 copies/mL. Throughout the two-year study period participants maintained viral loads between 3,500 and 10,700 copies/mL. Therapy cycles lasted a mean of about six months. Importantly, CD4 cell counts increased steadily from a baseline mean of 239 cells/mm³ to a mean of 323 cells/mm³ at 24 months. Only two participants experienced HIV disease progression.

While this strategy is still theoretical, attempts to define and harness reduced viral fitness for clinical benefit, and proof-of-concept case studies, will be followed with great interest. ViroLogic launched its Replication Capacity (RC) assay to measure viral fitness in June 2002, which may make such studies more feasible.

Designing a strategy for near-perfect adherence when taking salvage therapy can be as beneficial as having access to a new drug.

indinavir, 600 mg saquinavir, or 1,250 mg nelfinavir, all twice daily). Hydroxyurea (500 mg twice daily) was also included in 48 (71%) of the regimens. Of the 62 subjects included in the preliminary evaluation, one (2%) used six drugs, 40 (64%) used seven drugs, and 21 (34%) used eight drugs.

By week 8, those in the deferred treatment arm showed some evidence of reversion to wild-type virus similar to that observed in previous short-term treatment interruption studies. For example, 21%, 38%, and 24% of participants, respectively, showed evidence of a loss of at least one resistance mutation to the PI, NRTI, or NNRTI classes. Furthermore, 14%, 24%, and 7% of participants, respectively, experienced loss of resistance mutations to one, two, or three classes of drugs. However, 55% showed no evidence of reversal of resistance mutations.

Therapeutic drug monitoring of trough PI and NNRTI levels revealed that a slightly lower proportion of

participants achieved adequate drug levels in the immediate arm compared with the deferred arm (74% vs 80%). When results from resistance testing were correlated with either adequate or low drug levels, a better virological response was associated with reversal of resistance mutations when adequate drug levels were achieved.

Safety and tolerability are always a concern when dealing with regimens containing numerous drugs. Participants in this study generally experienced a low level of toxicity for a group with such advanced disease. Rates of grade 3 (severe) toxicities and HIV-related OIs were similar in the immediate and deferred arms, with slightly more events reported in the immediate treatment arm (although numbers were small).

Data from Dr. Montaner's mega-HAART cohort were presented at the XIV International AIDS Conference in Barcelona this past July. The results showed that this multidrug approach may produce a durable response with tolerable side effects. In this study 248

participants with multidrug-resistant HIV received regimens containing up to nine drugs (median of six). TDM was used to ensure adequate drug levels.

Using an intent-to-treat (ITT) analysis in which all participants were analyzed whether or not they continued in the study, 69% achieved viral loads below 400 copies/mL on at least two consecutive measurements and about 40% achieved viral load levels below 50 copies/mL by week 48. This response was sustained out to 24 months in 80% of those who achieved undetectable viral loads.

Dr. Montaner concluded that aiming for undetectable viral load in treatment-experienced people is both realistic and sustainable. Even more optimistically, he showed that using this aggressive, multidrug approach in individuals with highly drug-resistant HIV produced a survival benefit similar to that seen in treatment-naïve people using normal HAART regimens.

Strategies for Using New Drugs

Access to new drugs may provide the best hope for many people with HIV, especially those who continue to experience rising viral load levels after trying a mega-HAART combination. But the use of new medications requires careful consideration. In particular, it is important to avoid simply adding new drugs sequentially to an existing regimen as they become available. Adding a new drug to a regimen in which the existing medications are no longer effective is similar to using the new drug as monotherapy—a recipe for resistance. Some drugs in the development pipeline hold great promise, but they will produce better results if they are supported by other effective drugs in a combination regimen. (See "The HIV/AIDS Drug Pipeline," *BETA*, Summer/Autumn 2002, page 29.)

For each individual, weighing how long one can delay treatment with a new drug compared with how urgently one needs the medication can be very difficult. For people who have no other options and whose clinical health is at risk, any new drug may

Expanded Access Programs

Once new drug candidates have been shown to be generally safe and effective—but before they have been fully licensed—expanded access programs (EAPs) often make new medications available to people who need them most urgently. Availability of new drugs varies widely, and the timelines for expanded access can be difficult to predict. Activist organizations such as the Coalition for Salvage Therapy (CST) and the AIDS Treatment Activists Coalition (ATAC) lobby for EAPs. Reports on their progress can be found at www.atac-usa.org.

provide an important benefit—even if it is only for the short term.

Study results presented by Steven Deeks, MD, of the University of California at San Francisco (UCSF) and colleagues at the February 2002 Conference on Retroviruses and Opportunistic Infections (CROI) support the argument against changing treatment in the face of high-level resistance. Instead, people with high CD4 cell counts who are clinically well may stay on a “failing” PI combination, perhaps for several years. After 2–3 years on PI-based regimens, a subset of subjects who retained high CD4 cell counts (approximately 100 cells/mm³ above their nadir, or lowest ever count) despite viral load rebound have apparently maintained stable counts due to the reduced fitness of their drug-resistant virus. These individuals, who remain NNRTI-naive, will soon be able to use two drug classes in their next combination: NNRTIs and fusion inhibitors.

Delaying use of certain drugs in the hope of constructing a viable future regimen is not a straightforward option. Prediction of the timelines for pipeline drugs and expanded access programs is notoriously unreliable, and the cost of progressive accumulation of PI and NRTI resistance mutations is still not clear. Nevertheless, the results of Dr. Deeks’s study introduce the importance of viral fitness (see sidebar on page 24). Reports on viral fitness will likely increasingly become available for use in conjunction with the results of resistance and drug level tests, adding one more tool to help tailor antiretroviral treatment to each individual.

Experience Counts

The experience of physicians is an important factor in the success of salvage therapy. This past summer Mike Youle, MD, of the Royal Free and University College Hospital in London, who has been at the forefront of many new strategies to individualize patient care in the UK, began a presentation to the UK Community Advisory Board on

salvage therapy by stating, “There are lots of bad doctors, bad nurses, bad drugs, and bad patients,” and that if each of these problems were addressed, there would be little demand for salvage therapy. Dr. Youle clarified that lack of experience on the part of health-care providers, or an unwillingness to keep completely up-to-date on HIV treatment advances, directly affects the health and care of patients, an observation that has been supported by several studies.

People receiving HIV therapy—especially those with extensive treatment experience—should be treated by a physician who is aware of the most current research and is willing and able to develop individualized approaches to treatment. People with HIV should also keep up with the latest advances in treatment strategy and the availability of new drugs, so that decisions will be based on the best research available. Successful outcomes are often the result of collaboration and teamwork between informed patients and their physicians.

Summary

Look at lifetime resistance—
keep a history of drugs used in the past and previous resistance test results. These can be used to develop a worst-case “viral resistance” profile.

Maximize potency—
even if each drug only works a little, a mega-HAART combination can provide the combined potency many people need to reduce their viral load to an undetectable level.

Consider TDM—
suboptimal drug levels may explain why a past treatment regimen failed despite perfect adherence. Therapeutic drug monitoring may help determine optimal doses to overcome resistance or safely allow for drug interactions when using mega-HAART combinations.

Focus on adherence—
starting salvage therapy can be a good opportunity to devote attention to improved adherence. Count pills each day

and keep a strict pill diary. Think about nothing else until you get it right!

Try to improve tolerability—
when using multiple drugs, careful management of side effects such as nausea, diarrhea, and interrupted sleep becomes more important than ever. Report all adverse events to a health-care provider. Such symptoms can often be reduced using adjunct therapies such as anti-nausea or antidiarrhea medications or sleep aids.

Consider viral fitness—
new research shows that reduced viral fitness may be an important aspect of PI-resistant mutations. The possibility of frequently rotating drugs to maintain reduced viral fitness may be an option for the future.

Simon Collins (simon@i-Base.org.uk) is an HIV positive treatment advocate with HIV i-Base, an HIV positive peer support organization based in London.

This article has been adapted from a revised version of “Changing Treatment: A Guide to Second-line and Salvage Therapy,” a patient guide first produced in 1998 by HIV i-Base and updated every 4–6 months as new information becomes available. The guide is available at www.i-Base.org.uk.

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HIV ADVOCACY • GET INVOLVED •

AIDS Treatment Activists Coalition (ATAC)

- **ATAC** is a dynamic new
- coalition of people working
- together to improve HIV
- research and treatment
- access in the U.S.
- **ATAC** encourages greater,
- more effective involvement
- of all people with HIV in
- decisions—made by the
- pharmaceutical industry,
- government, and others—
- that affect their lives. To
- bolster the ranks of treat-
- ment activists, the coalition
- is committed to identifying,
- mentoring, and empower-
- ing new activists in all
- communities affected by
- the epidemic.

ATAC Contact Information

• Web site
• www.atac-usa.org

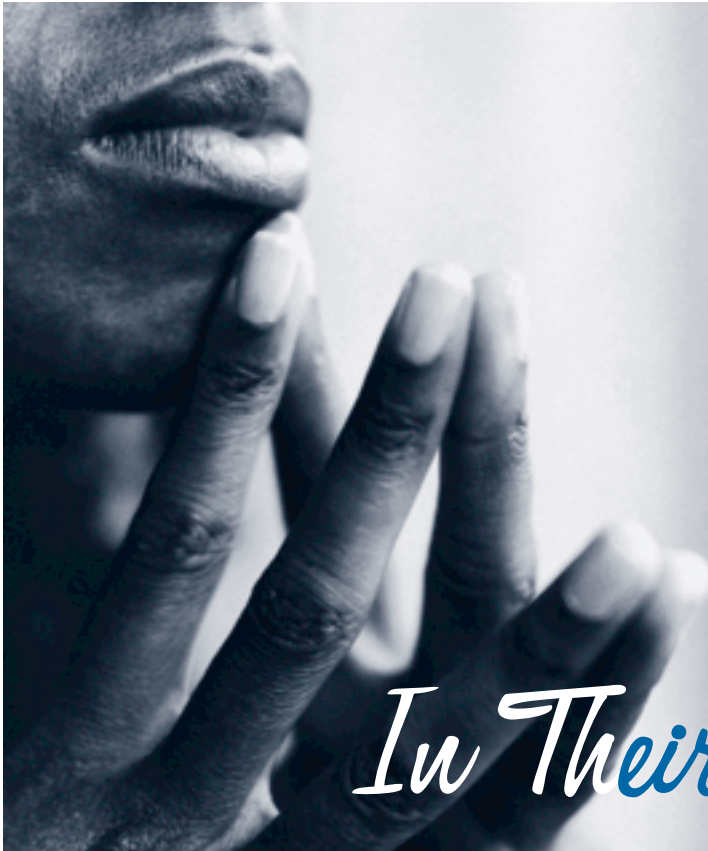
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In Their Own Words:

The Current State of Women and HIV

This edition of “Women and HIV” presents something different. Instead of exploring a topic through our customary method of secondary research, BETA asked women with HIV, women’s HIV treatment advocates, clinicians, and researchers for their views on the current state of health in HIV positive women. We posed a single question: What do you consider to be the most important treatment or health issues facing women with HIV today?

Leslie Hanna

Recurring themes included unique problems in accessing health care, antiretroviral drug toxicities, menopause, depression, and the need for research in women. Here are some of the responses, in the words of the respondents.

Amy Justice, MD, PhD

Associate Professor of Medicine, University of Pittsburgh School of Medicine

I think there are two major issues: helping women start and continue taking appropriate multidrug, multiclass antiretroviral therapy, and doing research to determine the degree to which treatment recommendations for men should be adjusted for women.

Access continues to be a huge issue. Women in 2002 still enter care later than men and, as a group, adhere less well to treatment than men. Today, it's not so much that providers will not or do not treat women, it's that women have real trouble with the basics of regularly accessing health care—they have trouble making and keeping appointments. Access is not something that is barred for women, but it is something that needs to be facilitated.

Drug toxicity is a huge issue we're only beginning to understand. Clearly it's a huge issue for men, too, but men and women may have different susceptibilities to many side effects. Diabetes is a good example. Women tend to have more body fat, and body fat is a predisposing factor for diabetes in the general population. What do HAART and HIV do to the picture for women? These and other questions, if answered, could improve routine monitoring—for instance, by informing better ways to use glucose and liver tests.

Liver health is a real concern. Women's livers work differently than men's. For example, we know that women are more susceptible to cirrhosis [liver scarring] when they consume the same amount of alcohol over the same amount of time, matched for weight—pound for pound—with men. We don't really know why, but the fact has been well demonstrated. Today, in HIV disease, a major cause of death is hepatitis and liver failure. Women with HIV are likely to be ethnic minorities and younger, inner-city residents with a high risk of smoking, alcohol use, and injection drug use. It's reasonable to ask whether these women might not be particularly susceptible to liver injury. This really needs to be studied.

Anne-christine d'Adesky

Treatment advocate

An issue that continues to bother me is antiretroviral dosing, and possibly overdosing, of women. Let's not forget that FDA approval [of anti-HIV drugs] has essentially all been based on dosing data gathered in male adults. There also have been a myriad of researcher observations, including published data, on differential initial viral loads and CD4 cell counts in women, and there are different patterns of drug toxicity in women as well.

Rebecca Denison

Founder of WORLD (Women Organized to Respond to Life-threatening Diseases), treatment advocate, and HIV positive woman

1. Hormones and HIV, including hormone replacement therapy (HRT) options,
2. Metabolic complications and other side effects of medications, and
3. Structured treatment interruptions.

These are high on my list today; tomorrow it will probably be something else.

Priscilla Abercrombie, RN, NP, PhD

Assistant Clinical Professor, Department of Family Health Care Nursing, University of California at San Francisco (UCSF)

I've been following women with abnormal Pap smears for many years. Nothing's changed; HPV [human papillomavirus] is still a huge problem. We're still treating it the same way, and following women very carefully over time. We're not yet sure if HAART is helping to decrease the number of abnormal Pap smears or if it's improving the status of women with cervical dysplasia [abnormal cells]. But the majority of women—at least 50%—will have an abnormal Pap smear at some point, and for most women HPV is a recurrent, persistent disease. The rates of cervical cancer have not changed, though.

Some women we've been treating for years are now entering menopause. While the signs and symptoms of menopause in HIV positive women are similar to those in HIV negative women, there are some unique treatment complications (mostly liver complications), and there are concerns about antiretroviral drug interactions and hormone replacement therapy. We need to learn more about how best to manage menopause in women with HIV who are taking HAART. [A study of HPV and HAART is currently enrolling in several cities. See page 49 for details.]

Eve W.

HIV positive woman

I am very concerned about the long-term toxicity of the antivirals. As a woman on treatment for close to ten years, I've had a hard time dealing with the side effects. Although none have been life-threatening, they started to really wear me down and scare me. On top of this, adherence became more difficult over time. I just got sick of taking the medications day after day. I felt I was pushed to start treatment all those years ago. Hopefully things are different now.

I would say the most important thing is to develop medications that are less toxic and easier to take for the long term. Also, women need to be educated about their options, so they can decide if and when they should start medications and be fully aware of what they are getting into—side effects and all.

One last thing that is important to me as an HIV positive woman is that HIV did not take away my right to have a child. Women should not give up on having a family if that is what they want.

Maureen Shannon, MS, FNP, CNM

Associate Clinical Professor, Department of Family Health Care Nursing, UCSF

There are multiple issues because there are so many different women with HIV disease who have acquired the virus in different ways, and because it's a very complicated disease. There are some major themes, though.

First, although things have changed, there is still a strong stigma associated with this disease, especially for women. It's still so shameful to have HIV/AIDS that some women delay seeking services or treatment just for that reason. By trying to conceal their status, they'll end up receiving suboptimal care. Even in the San Francisco Bay Area, let alone the rest of the world, there's a prevailing attitude toward women of, "What did you do to get this disease?" Many women today do not tell their families or their coworkers or neighbors. Stigma may be subtler in the U.S., but I've known positive women who give birth to babies they hope are HIV negative, who then have to go to a pediatrician—and the judging begins, or so it's perceived. Just having to discuss the babies' HIV-related concerns reflects on the mom, and it's not like discussing diabetes or herpes. It's just not.

Another important issue for women, and one that affects access, is the amount of violence that so many women experience, especially at the hands of intimate partners. This includes both psychological and physical threats. HIV positive women also have a very high rate of past childhood abuse, including sexual assault and molestation. As providers we're more aware of this today than we were earlier in the epidemic, but clinicians still do not screen for violence as much as they should. Yet doing so can make a huge difference when making treatment decisions. For example, you have to be very careful when interpreting depression in women—is it related to HIV? to medication side effects? to current violence, or a childhood history of sexual assault? Women living with violence or with a history of violence often have a condition similar to post-traumatic stress disorder, but since they're not often screened for any of this, they don't often receive the appropriate care. Such women often self-medicate, too, and it's important for us as providers to know why. Violence also impacts women's entry into care and adherence to care. We discuss safety

plans on a regular basis with many of our women clients—for instance, do they have a supply of medications and a suitcase ready to go in case they need to leave a dangerous situation in a hurry? Finally, women with so much violence in their lives also may end up spending time in jail or otherwise incarcerated, which has implications for access to medicines.

A somewhat related issue is the lack of mental health services. Women with HIV have a high rate of depression and chronic stress, along with abuse. In general, there aren't a lot of psychological services available for anyone these days, but what does exist tends to be focused on people with severe mental illness. It would be great to have services available to women earlier in challenging situations—during periods of new or significant stress—to teach coping and problem-solving skills. Instead, we tend to throw drugs at people and hope for the best, i.e., without providing counseling. We don't hesitate to order an expensive CT scan, but we don't generally support psychological needs and services.

Grace McComsey, MD

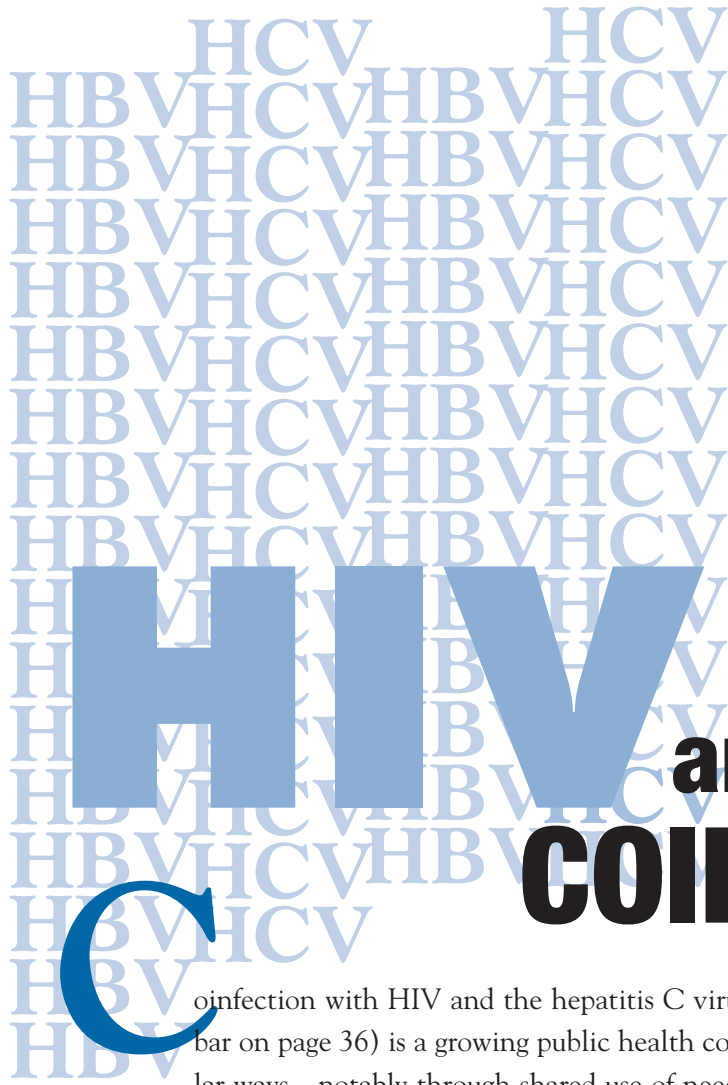
Assistant Professor of Medicine and Pediatrics, Case Western Reserve University School of Medicine

Several things come to mind. The most important thing is probably the fact that we need studies focused on women. If we want answers to questions about women, we cannot get the data we need from men. This is true whether you're talking about antiretroviral treatments or side effects.

Here in Cleveland we are beginning a study that involves two months of complicated treatment, requiring participants to be seen frequently, to use study medications that need to be taken three times daily, and at study's end to have muscle and fat biopsies. This is a study that might have been difficult to enroll anyone in, yet we have so far enrolled 60% women (18 of 30 total). We also have more women than men on the waiting list.

How have we enrolled so many women? What works is not mysterious: we simply spend the time necessary to explain and discuss what the study is trying to achieve and why it's important. When women understand that there are more complications in women than in men, and once they understand the purpose and benefits of the study to themselves and to HIV medicine, they are usually very interested in participating. I also give talks at different community groups and forums, some of which are focused on women. In the days following a talk, women have tracked me down at the clinic, asking for more information and how to enroll. So our efforts to educate about special issues relating to women have sometimes yielded very good results.

Leslie Hanna is the former editor of BETA.



Liz Highleyman

HIV and Hepatitis COINFECTION



oinfection with HIV and the hepatitis C virus (HCV) or hepatitis B virus (HBV, see sidebar on page 36) is a growing public health concern. Because the diseases are spread in similar ways—notably through shared use of needles to inject drugs and sexual activity—many people are coinfecting with HIV and HCV, HIV and HBV, or even all three viruses.

Hepatitis C and hepatitis B are viral infections of the liver; over time they can lead to serious consequences including liver cirrhosis and liver cancer. Most studies show that HIV infection leads to more aggressive hepatitis C or hepatitis B and a higher risk of liver damage. Studies of how HCV and HBV affect HIV disease are less clear. Most research shows that HCV does not accelerate HIV disease progression, but HIV/HCV coinfection may impair immune system recovery after starting antiretroviral therapy.

Coinfection can complicate treatment. People with liver damage due to chronic hepatitis are more likely to experience hepatotoxicity (liver toxicity) related to anti-HIV drugs. In addition, drugs used to treat HIV and hepatitis can interact and side effects may be exacerbated. Most experts recommend that HIV should be controlled first before a person begins HCV treatment. With careful management, most people with HIV/HCV or HIV/HBV coinfection can be successfully treated for both diseases. In fact, several recent studies suggest that HIV/HCV-coinfecting people with well-controlled HIV disease and relatively high CD4 cell counts may do as well as those with HCV alone.

HIV/HCV: A Growing Public Health Problem

Coinfection refers to infection with two or more different disease-causing organisms. Hepatitis C is a common coinfection in people with HIV. An estimated 200,000–300,000 people in the U.S. have both HIV and HCV. Experts believe that about 25% of Americans with HIV also have HCV; conversely some 10% of people with HCV are thought to also have HIV. In an analysis published in the March 15, 2002 issue of *Clinical Infectious Diseases*, Kenneth Sherman, MD, of the University of Cincinnati, Ohio, and colleagues found an overall HCV prevalence rate of 16% in a cohort of people with HIV; in different subpopulations coinfection rates ranged from 3% to 73%.

HIV/HCV coinfection is increasingly recognized as a growing public health problem. Early in the HIV/AIDS epidemic most people with HIV were expected to die from AIDS, and less attention was devoted to other long-term conditions. Because chronic hepatitis C progresses so slowly, many HIV positive people who were infected with HCV in the 1970s or 1980s are only now beginning to develop advanced liver disease. At several recent conferences a number of presentations were devoted to HIV/HCV coinfection. David Thomas, MD, from Johns Hopkins University in Baltimore, Maryland, reviewed the current state of knowledge about HIV/HCV coinfection at a June 2002 meeting convened by the National Institutes of Health (NIH) to generate a new consensus statement about HCV treatment, care, prevention, and future research.

As improved HIV treatment has reduced mortality due to opportunistic illnesses (OIs), liver failure—often related to chronic viral hepatitis—has become a major cause of hospitalization and death in people with HIV/AIDS. In some recent studies liver failure due to HCV was the leading cause of death.

Several studies at the 9th Conference on Retroviruses and Opportunistic Infections (CROI) held in February 2002

looked at illness and death in HIV/HCV-coinfected people. Ronald Reisler, MD, MPH, of the NIH and colleagues reported that the rates of severe (grade 4) adverse events and death were higher in HIV positive people coinfecting with HCV or HBV than in those with HIV alone. David Rimland, MD, of the Atlanta Veterans' Administration Medical Center and colleagues showed that coinfecting people had shorter survival times after an HIV or AIDS diagnosis than those with HIV alone. Kelly Gebo, MD, of Johns Hopkins and colleagues found that HIV/HCV coinfection substantially increased the likelihood of hospitalization compared with those who had only HIV. On the other hand, Ellen Tedaldi, MD, of Temple University in Philadelphia and colleagues reported that after controlling for CD4 cell count, survival rates were comparable in HIV/HCV-coinfected people and those with HIV alone, suggesting that effective HIV treatment can minimize the detrimental effects of HCV coinfection.

Because the presence of HIV accelerates the progression of hepatitis C, HCV is thought of as an OI in people with HIV; however, it is not considered an AIDS-defining illness.

The “Twin Epidemics”

HCV and HIV share many characteristics. Both are blood-borne RNA viruses that replicate rapidly. The two viruses also share similar transmission routes. Direct blood-to-blood transmission—for example through needle sharing—is the most efficient means of transmitting both viruses. Among some populations of injection drug users, the HIV/HCV coinfection rate may be as high as 90%. Coinfection is also common among hemophiliacs and others who received repeated blood product transfusions before such products were heat-treated to inactivate pathogens. Some people contracted HCV through blood transfusions before the early 1990s. A reliable HCV blood test became widely available in 1992. The rate of HIV/HCV coinfection is also high among prisoners.

Along with these similarities, there are also several differences between

the two viruses. HCV, unlike HIV, does not integrate into human cells and is thus easier to eradicate. HCV is less likely than HIV to be transmitted sexually or from mother to child during pregnancy, birth, or breast-feeding. According to the Centers for Disease Control and Prevention (CDC), people who contracted HIV through sexual activity have HCV infection rates similar to those of the adult population as a whole (estimated at under 3% for people in monogamous heterosexual relationships, but somewhat higher among gay men and people with multiple sex partners).

However, studies show that the risk of sexual or perinatal transmission of HCV is greater if a person also has HIV—possibly due to the fact that HIV/HCV-coinfected people tend to have higher HCV viral loads. Recent data reported by researchers from Chelsea and Westminster Hospital in London suggest that sexual transmission is responsible for an increasing proportion of HCV infections among people with HIV. And while 5% or less of HCV-infected mothers without HIV transmit HCV to their infants, among HIV/HCV-coinfected mothers the transmission rate may be three times as high.

Because many people are coinfecting with HCV and HIV, the U.S. Public Health Service and the Infectious Disease Society of America recommend that all people with HIV should be screened for HCV. Detecting HCV in people whose immune systems are severely compromised can be difficult because they may not produce enough antibodies to show up on a test. In HIV positive people with a CD4 cell count over 200 cells/mm³, a standard HCV antibody test is usually sufficient; if the CD4 cell count is below 200 cells/mm³, an HCV RNA viral load test may be necessary to diagnose hepatitis C.

Hepatitis C Basics

Hepatitis C is a slowly progressing disease of the liver. Because this organ carries out some 500 bodily functions, damage to the liver can lead to a variety of symptoms and associated

conditions. HCV was identified only in 1989; before that it was known as non-A/non-B hepatitis. In some people infected with HCV the immune system can completely eradicate the virus, but in an estimated 80% of infected people hepatitis C becomes chronic (lasting more than six months). HCV is most often spread through contaminated needles used to

Antibody tests (ELISA and RIBA) are used to detect whether a person has been infected with HCV. Genotype tests are used to determine what strain of HCV a person has. There are six known HCV genotypes; 1a and 1b, which are most common in the U.S., are more difficult to treat. Liver enzymes, in particular alanine transaminase (ALT) and aspartate transaminase (AST), are

Pegasys) is a new, chemically altered form of interferon that lasts longer in the body and appears to work better than standard interferon.

Recent studies show that combination therapy with pegylated interferon plus ribavirin can clear HCV in about 50% of HIV negative people with genotype 1 and about 80% of those with genotypes 2 or 3. As discussed below, treatment response rates tend to be lower in people coinfecting with HIV. Traditionally, HCV therapy is administered for a specified period of time (usually 6–24 months) and discontinued if HCV viral load does not decrease. However, experts increasingly believe that treatment may reduce liver damage even if HCV viral load does not become undetectable. A trial called HALT-C is now underway to study the possible benefits of long-term HCV maintenance therapy.

Side effects of interferon are common, and may include fever, fatigue, headaches, flu-like symptoms, muscle aches, low blood cell counts, and irritability or depression. Ribavirin may cause hemolytic anemia (destruction of red blood cells) and birth defects.

How HIV and HCV Interact

The Impact of HIV on HCV

HIV/HCV coinfection is still poorly understood, but recent research has shed light on how the two viruses interact. In the February 2002 issue of *Current Gastroenterology Reports*, Andrew Talal, MD, MPH, from Cornell University's Weill College of Medicine in New York City and colleagues reviewed the pathophysiology of HIV/HCV coinfection. According to the authors, a strong cell-mediated immune response involving both CD4 and CD8 cells is required to keep HCV under control. A strong immune response also appears necessary to enable successful HCV treatment with interferon. In people with HIV, the immune response may be compromised, making it less likely that an infected person will clear HCV and allowing HCV to replicate more rapidly.

Not everyone with HCV needs to be treated. Many different factors—such as a person's age, how long he or she has been infected, HCV genotype, and extent of existing liver damage—should be taken into account when deciding whether to treat.

inject drugs. Tattoo needles and shared personal items such as razors and toothbrushes may also spread the virus. As discussed above, HCV transmission through sexual contact or from mother to infant are uncommon, but do occur.

Most people with acute or chronic HCV have no symptoms. Those that do may experience fatigue, nausea, loss of appetite, abdominal pain, and a flu-like feeling. An estimated 10–25% of people with chronic HCV develop severe liver disease—usually after 10–40 years—which may include liver inflammation, fibrosis (the development of tough, stringy tissue in the liver), cirrhosis (scarring), hepatocellular carcinoma (liver cancer), and liver failure. A minority may develop jaundice (yellowing of the skin and whites of the eyes). When people develop decompensated cirrhosis, scar tissue blocks the flow of blood through the liver and the organ is no longer able to function properly. This can lead to serious conditions such as bleeding veins (varices) in the esophagus or stomach, abdominal swelling (ascites), and brain dysfunction (hepatic encephalopathy). Liver failure due to HCV is the leading reason for liver transplants in the U.S.

measured as an indication of liver inflammation. Many—but not all—people with chronic hepatitis have elevated liver enzyme levels. Viral load tests (PCR, bDNA, and TMA) measure the amount of HCV genetic material (RNA) in the blood, and can help indicate whether treatment is working. In contrast with HIV, HCV viral load is not correlated with disease severity.

Liver biopsy, in which a small sample of tissue is withdrawn using a needle and examined under a microscope, is considered the “gold standard” for gauging the extent of liver damage. Biopsies are used to help make decisions about whether treatment is needed. Liver tissue damage is graded on a scale of 0–4. Although several tests are under study, there currently is no reliable noninvasive means of detecting liver fibrosis.

Not everyone with HCV needs to be treated. Many different factors—such as a person's age, how long he or she has been infected, HCV genotype, and extent of existing liver damage—should be taken into account when deciding whether to treat. The usual treatment for HCV is a combination of interferon-alpha (Intron-A or Roferon-A) plus ribavirin (Rebetol, Copegus). Pegylated interferon (Peg-Intron or

Much of the liver damage related to hepatitis C is caused not by the virus itself, but rather by the immune system's response to HCV. Thus, it might be expected that people with compromised immune systems would mount a weaker immune response that causes less liver tissue damage. However, research indicates that the opposite seems to be the case.

Most studies show that HCV disease progression is more rapid in HIV/HCV-coinfected people and is more likely to lead to severe liver damage. Many studies show higher rates of cirrhosis in coinfecting individuals. For example, at the November 2001 meeting of the American Association for the Study of Liver Disease, Vincent di Martino, MD, and colleagues with the French MULTIVIRC study team reported that coinfecting people died earlier than those with only HCV because they progressed to cirrhosis sooner. At the XIV International AIDS Conference held in Barcelona this past July, A.H. Mohsen from St. Thomas School of Medicine in London and colleagues estimated that the average time between HCV infection and the development of cirrhosis is 22 years in coinfecting people compared with 33 years in those with HCV alone—a 1.5-fold increase in the rate of liver disease progression.

At the June NIH consensus meeting Dr. Thomas cited a meta-analysis showing that HIV/HCV-coinfected people had a two-fold greater risk of progression to cirrhosis and a six-fold greater chance of developing end-stage liver disease. Javier Garcia-Samaniego from Madrid, Spain, and colleagues reported in the January 2001 issue of the *American Journal of Gastroenterology* that HIV/HCV-coinfected individuals had a higher rate of hepatocellular carcinoma than people with HCV alone. In addition, most research indicates that HIV/HCV-coinfected people typically have higher HCV viral loads than those with only HCV.

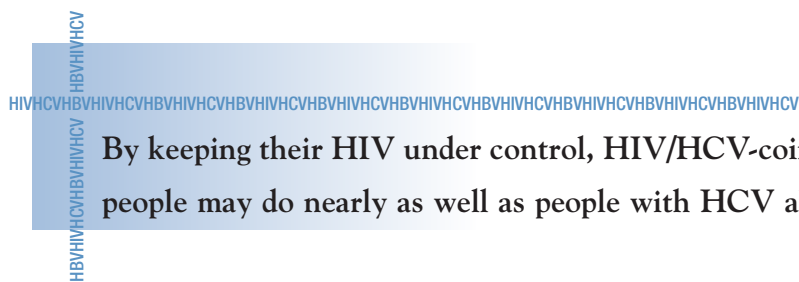
Importantly, the longer-term studies of HIV/HCV coinfection were initiated prior to the widespread use of highly active antiretroviral therapy

(HAART), and many of the participants had low CD4 cell counts. More recent research suggests that the differences in HCV disease progression between coinfecting people and those with HCV alone may not hold for people who have well-controlled HIV and whose immune systems remain relatively intact with high CD4 cell counts. For example, Yves Benhamou, MD, and colleagues, also with the MULTIVIRC team, reported in the October 1999 issue of *Hepatology* that HIV/HCV coinfection, having a CD4 cell count below 200 cells/mm³, and heavy alcohol consumption were all associated with a greater likelihood of HCV disease progression. But HIV/HCV-

years, and 9% vs 27% at 25 years). This and other research suggests that by keeping their HIV under control, HIV/HCV-coinfected people may do nearly as well as people with HCV alone.

The Impact of HCV on HIV

The impact of HCV on HIV disease is less clear, and study results are conflicting. However, a majority of research indicates that HCV does not increase HIV viral load or directly accelerate HIV disease progression. For example, Mark Sulkowski, MD, of Johns Hopkins and colleagues reported at the Barcelona AIDS conference and in the July 10, 2002 issue of the *Journal*



coinfecting participants with over 200 cells/mm³ had hepatitis C progression rates similar to those of people with HCV alone.

Massimo Puoti, MD, and colleagues with the HIV-HCV Coinfection Study Group reported in the January 1, 2001 issue of the *Journal of Infectious Diseases* that the presence of fibrosis was associated with CD4 cell counts below 500 cells/mm³, whether or not a person had HIV. And at the Barcelona AIDS conference C. Arizcorreta and colleagues from Cadiz, Spain, presented research showing that both lower CD4 cell counts and higher HIV viral loads were associated with worse liver damage in coinfecting individuals.

In a study published in the August 2001 issue of *Hepatology*, Dr. Benhamou's team reported that people receiving antiretroviral regimens that included a protease inhibitor (PI) had lower fibrosis scores and lower rates of progression to cirrhosis than those who had not taken PIs (2% vs 5% progression rate at five years, 5% vs 18% at 15

of the *American Medical Association (JAMA)* that among their cohort of nearly 900 HIV/HCV-coinfected people, those with both viruses were not more likely to experience accelerated HIV disease progression, develop an AIDS-defining illness, or die from AIDS. HCV coinfection did not appear to reduce the effectiveness of HAART, and the researchers concluded that HCV should not be seen as a barrier to HIV treatment. Notably, in this cohort coinfecting people were less likely than those with HIV alone to be taking HAART, and most deaths occurred in the untreated subjects.

Similarly, Dr. Rimland's team reported in the July 1999 issue of *Clinical Infectious Diseases* that HIV/HCV coinfection appeared to have no effect on the progression of HIV disease or survival in 100 coinfecting people treated between January 1992 and May 1997. Dr. Rimland concluded that there was "absolutely no difference" in HIV disease progression and survival—as assessed by time from HIV

HCV treatment response rates tend to be lower in coinfecting people than in those with HCV alone.

Pegylated interferon plus ribavirin is currently the most effective HCV treatment option.

HIV Treatment in People with HCV

HIV/HCV coinfection can complicate HIV treatment due to adverse drug effects. These complications are of two types:

1. **Hepatotoxicity**—liver-specific side effects of antiretroviral drugs, which may be worse in people with existing liver damage due to chronic hepatitis.
2. **Drug interactions**—in which anti-HIV and HCV drugs that have similar side effects produce intensified (additive or synergistic) adverse events when the drugs are used together.

Hepatotoxicity

Many anti-HIV drugs are metabolized by the liver. When drugs are taken in high doses—and especially when different drugs are combined—they can cause liver injury. This is especially likely in people who have existing liver damage due to chronic viral hepatitis or other factors such as heavy alcohol consumption. For example, Dr. Sulkowski and colleagues reported in the January 2002 issue of *Hepatology* that 69% of the cases of severe liver toxicity seen in their study of HIV positive people taking nevirapine (Viramune) or efavirenz (Sustiva) occurred in people coinfecting with HCV or HBV. Research also suggests that women are more likely to experience drug-related hepatotoxicity, perhaps due to their lower average body weight.

Drug-related liver injury is often signaled by increased levels of liver enzymes, in particular ALT and AST. In fact, when combination antiretroviral

therapy was first used many physicians noticed dramatic increases in their patients' liver enzyme levels and began testing them for hepatitis C—thus revealing that HIV/HCV coinfection was more common than previously suspected. Mild-to-moderate hepatotoxicity is usually asymptomatic, but some people may experience nausea, fatigue, itching, or elevated bilirubin (bile pigment) levels leading to jaundice. Elevated liver enzyme levels are most common soon after starting a new drug and typically stabilize over time, but in

some cases hepatotoxicity develops after a longer period on therapy.

Different studies have shown that antiretroviral regimens on the whole are associated with a two-fold to five-fold increased risk of hepatotoxicity. All classes of anti-HIV drugs have been linked with liver toxicity. Most studies show that the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine and the PI ritonavir (Norvir) at full dosage are the worst offenders; the small amounts of ritonavir sometimes added to regimens to “boost” blood levels of other PIs are

HEALTHY Liver Tips

- Get vaccinated against hepatitis A and hepatitis B.
- Avoid alcohol. Many studies show that alcohol contributes to liver damage, especially in people with chronic viral hepatitis.
- Be cautious about using prescription drugs, over-the-counter medications, street drugs, and herbal remedies. Be especially careful when combining different drugs. Tell health-care providers about all drugs and herbs being used.
- Avoid exposure to environmental toxins such as solvents, paint thinners, and pesticides. If it is necessary to use such chemicals, work in a well-ventilated area and wear gloves and a protective face mask.
- Eat a healthy, well-balanced diet.
- Get regular, moderate exercise.
- Sleep enough at night and rest during the day as needed to help manage fatigue.
- Get regular health check-ups, including monitoring of liver enzymes and blood cell counts.

SUMMARY

HIV can be successfully treated in most coinfected people.

Hepatotoxicity and drug interactions can complicate HIV treatment in coinfected individuals.

Medication regimens often can be adjusted to minimize adverse events; do not adjust doses or change drugs without medical advice. Report all new or worsening symptoms to a health-care provider.

Future Directions

Therapies for both HIV disease and hepatitis C have improved dramatically in the past five years. In fact, several lessons learned from treating HIV have been fruitfully applied to the development of therapies for HCV. It is increasingly apparent that for HCV, as for HIV, regimens of multiple drugs that work by different mechanisms are more effective than monotherapy. In contrast to anti-HIV drugs that target specific viral enzymes, current treatments for hepatitis C are nonspecific. However, new drugs that target the HCV protease and helicase enzymes are under development and may provide better future treatment options. Unlike HIV, HCV does not integrate itself into human cells, and therefore may be more easily eradicated. The latest treatment regimen, pegylated interferon plus ribavirin, produces sustained viral clearance in one-half or more of people with HCV alone. Researchers are exploring the use of long-term maintenance therapy, as is done for HIV, in an effort to reduce hepatitis C disease progression and prevent liver damage.

Liz Highleyman (liz@black-rose.com) is a freelance medical writer and editor based in San Francisco.

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CORRECTION NOTICE

The telephone number listed for the T-20 (enfuvirtide, Fuzeon) expanded access program in the Summer/Autumn 2002 issue of *BETA* was incorrect. Instead, visit www.T20EAP.com for more information.

Trial results presented by Giorgio Barbarini, MD, and colleagues at the XIV International AIDS Conference and mentioned in the Summer/Autumn 2002 issue (“Cardiovascular Disease in People with HIV”) have been withdrawn by the study authors following a request to verify the originality of their data. The study had appeared to show an association between protease inhibitors and cardiovascular disease.

Note should have been made in the Summer/Autumn 2002 issue that Lisa Garbus, MPP, author of the “HIV/AIDS in Asia and the Pacific” article, is no longer an editor at HIV InSite. Since March 2002 she has been director of the Country AIDS Policy Analysis Project at the AIDS Policy Research Center at the University of California at San Francisco. The article reprinted in *BETA* was last updated in December 2001 and did not reflect new data released since then, including revised national adult HIV prevalence figures issued by UNAIDS in July 2002.

OPEN Clinical TRIALS

FOR HIV/AIDS TREATMENTS

Liz Highleyman

Below is a partial listing of currently enrolling U.S. clinical trials gathered from various sources. Two of the main clinical trial resources have recently undergone significant changes. In the summer of 2002 HIV InSite's Trials Search database of clinical trials was replaced with TrialScope, a directory of organizations that conduct HIV/AIDS-related research. It provides contact information for each research site, the types of research each site conducts, links to organizational web sites, and any affiliations with major multicenter research groups. TrialScope is available at hivinsite.ucsf.edu (enter "TrialScope" in the search field); users select their desired state from a scroll-down list.

AIDSinfo, a new web site of the U.S. Department of Health and Human Services (DHHS), allows users to search for HIV/AIDS-related studies in a database maintained by ClinicalTrials.gov, a clinical trial listing for all diseases. The database may be accessed at either www.aidsinfo.nih.gov or www.clinicaltrials.gov. AIDSinfo also offers a toll-free telephone help line at 800-448-0440 (TDD/TTY 888-480-3739; international callers should dial 301-519-0459). Specialists are on hand Monday through Friday from 12:00 pm to 5:00 pm ET (9:00 am to 2:00 pm PT) to help locate trials and answer questions.

The AIDS Community Research Initiative of America (ACRIA) maintains a directory of HIV/AIDS clinical trials in New York state, New Jersey, Connecticut, and Philadelphia, and may expand to other areas of the country in the future. The ACRIA directory is available at www.criany.org/acria.html.

Call the telephone numbers below for more information about specific trials and a listing of study sites. Protocol (study) numbers, if available, are provided in parentheses at the end of each trial description.

Antiretroviral Therapy

Salvage Therapy: Dual vs Triple PIs

This study will compare a salvage (or "rescue") regimen containing three protease inhibitors (PIs) with two

different combinations containing two PIs. The study will examine safety, tolerability, effectiveness, and blood drug levels, and will look at whether "boosting" PI drug levels with ritonavir (Norvir) can improve treatment response. Participants will be randomized to receive lopinavir plus ritonavir (Kaletra); ritonavir plus GW433908, Glaxo-SmithKline's new PI candidate; or lopinavir, ritonavir, and GW433908. All participants will also take one or two nucleoside reverse transcriptase inhibitors (NRTIs) and tenofovir DF (TDF, Viread); the NRTIs are not provided by the study. Blood will be drawn and tested for drug levels at weeks 12, 24, and 48. A substudy (A5174S) will conduct more intensive sampling of blood drug levels; the first 20–25 participants enrolled in each arm will also be enrolled in the substudy.

Participants must be at least 18 years of age, have been on antiretroviral therapy for a total of at least one year, and have a viral load above 500 copies/mL within 60 days of prestudy screening despite being on a stable (unchanged) anti-HIV regimen for at least 12 weeks. Exclusion criteria include previous use of both lopinavir and amprenavir (Agenerase) for more than seven days each; untreated serious illnesses; or use of other experimental drugs, cancer chemotherapy, or immune-modulating drugs within 30 days of study entry. Women must not be pregnant or breast-feeding.

There are over 30 study sites including Atlanta (404-616-6313), Boston (617-726-3819), Chapel Hill (919-843-8761), Chicago (312-942-5865), Cleveland (216-844-8051), Denver (303-372-5535), Los Angeles (323-343-8283), New York City (212-305-2665), San Francisco (415-514-0550 ext. 362), and Seattle (206-731-8877). (ACTG A5143/A5147S)

Salvage Therapy: Indinavir plus Ritonavir

This randomized, open-label study will examine the safety and tolerability of indinavir (Crixivan) plus ritonavir as salvage therapy in participants who have experienced treatment failure with amprenavir, nelfinavir (Viracept), or

saquinavir (Fortovase or Invirase). The study will look at the pharmacokinetics (absorption, metabolism, and excretion) of indinavir and ritonavir, and assess the side effects of the two drugs. Researchers hope to determine whether “boosting” indinavir levels with ritonavir can allow indinavir to be taken twice rather than three times daily and at lower doses. Participants will be randomized to receive one of two different doses of indinavir with ritonavir for 24 weeks; all will also take two NRTIs (not provided by the study). Viral load and other measurements will be assessed at weeks 1, 2, 4, 8, 12, 16, 20, and 24. The week 2 evaluation will include an extensive pharmacokinetics analysis and will require a 12-hour hospital stay. Participants who experience virological failure during the trial may elect to either remain on treatment and be followed for 24 weeks, or else discontinue treatment.

Participants must be at least 18 years of age and have a viral load between 500 and 100,000 copies/mL within 45 days of study entry. They must have taken an antiretroviral regimen that includes two NRTIs plus nelfinavir, saquinavir, or amprenavir for at least 12 weeks before study entry. There must be at least one NRTI that has not been taken for more than 14 days, or never taken at all in the case of 3TC (lamivudine, Epivir). Exclusion criteria include taking any PIs other than those listed above or having HIV that is resistant to indinavir or ritonavir. Subjects must not have taken non-nucleoside reverse transcriptase inhibitors (NNRTIs), experimental drugs, or immune-modulating drugs within 30 days of study entry. Subjects also must not have had any active opportunistic illnesses (OIs), infections that require treatment, or fever within 14 days of study entry, or any cancers that require chemotherapy. Women may not be pregnant or breast-feeding. Finally, subjects must be willing and able to drink 1.5 liters of water or other fluids each day.

Study sites include Baltimore (410-955-4370), Birmingham (205-975-7925), Indianapolis (317-274-8456), New York City (212-420-4432), Philadelphia (215-349-8092), and San Francisco (415-476-9296 ext. 350). (ACTG A5055)

Salvage Therapy: T-20 and STI

This randomized, open-label study will compare immediate salvage therapy using combination antiretroviral therapy plus T-20 (enfuvirtide, Fuzeon) with a 16-week structured treatment interruption (STI) followed by combination therapy plus T-20. The study will examine whether STI helps improve the chances of successful treatment in people who have HIV that is resistant to multiple drugs. Virological response will be measured at weeks 16, 32, and 48. All participants will receive T-20 either immediately or after 16 weeks; T-20 is administered by subcutaneous (under the skin) injection twice daily. The other drugs in each subject’s regimen should be the strongest antiretroviral combination available.

Participants must be at least 18 years of age and have used NRTIs, NNRTIs, and PIs. They must have been on continuous antiretroviral therapy for the 24 weeks before study

entry, with no regimen changes in the preceding 12 weeks (except for substitutions within the same drug class due to toxicity). Participants must have experienced failure of at least one highly active antiretroviral therapy (HAART) regimen before study entry, and must have had a viral load greater than 500 copies/mL within the four months preceding the study. Those who experienced virological failure on their first HAART regimen are not eligible. Recent genotypic resistance testing must show at least two major mutations conferring resistance to NRTIs or PIs; participants must also show evidence of current or prior NNRTI resistance. Exclusion criteria include previous use of T-20 or T-1249; unstable HIV disease that increases risk of disease progression during the STI; an active, untreated OI or unexplained fever; active hepatitis C requiring treatment; cancer requiring chemotherapy; or other severe illness. Women must not be pregnant or breast-feeding.

This study is offered through the University of California at San Francisco (UCSF). For information contact Anna Smith, RN, at 415-476-9296 ext. 330.

STOP: Predictors of Progression during STI

Current federal HIV treatment guidelines recommend that therapy be started when CD4 cell counts fall below 350 cells/mm³. Recent research suggests that people with CD4 cell counts above this level may be able to safely discontinue antiretroviral treatment. This prospective, observational study will look at predictors of immunological and clinical disease progression in participants with CD4 cell counts above 350 cells/mm³ who stop antiretroviral therapy. In step 1, participants will discontinue anti-HIV therapy when they enter the study, for a maximum of 96 weeks. Viral load, CD4 cell counts, immunological function, neurocognitive (mental) changes, metabolic measurements, anthropomorphic (body shape) changes, health-care utilization, and quality of life will be assessed over the course of the study. Participants and their primary care providers will decide if and when to restart anti-HIV therapy; those who do so will be followed for an additional 24 weeks or until week 96 (step 2). This study does not provide any medications.

Participants must be at least 13 years of age and have been taking stable antiretroviral treatment for at least six months before study entry. They must have had a pretreatment CD4 cell count above 350 cells/mm³; in addition, they must have had a CD4 cell count above 350 cells/mm³ and a viral load below 55,000 copies/mL within 45 days of study entry.

Study sites include Dallas (214-590-0414), San Francisco (415-514-0550 ext. 354), and Stanford (650-723-2804). (ACTG A5170)

OPTIMA: Mega-HAART and STI

This study, conducted jointly by researchers in the U.S., the UK, and Canada, will examine the benefits of

“mega-HAART” regimens in people for whom treatment with NRTIs, NNRTIs, and PIs has failed. It will also look at whether a three-month break from treatment can help reduce drug resistance and allow people to better tolerate therapy. Some participants will be randomized to receive mega-HAART regimens containing five or more anti-HIV drugs, while others will take standard HAART regimens of up to four drugs. Drugs will be selected by a participant’s own provider, guided by genotypic resistance testing. In addition, some subjects will be randomized to undergo a three-month antiretroviral drug-free period. Outcomes to be measured will include viral load, immunological function, time to serious side effects, time to AIDS-defining illness, and survival time. Subjects will be followed for an average of two years.

Participants must be at least 18 years of age, have been on continuous HAART for at least three months, and have experienced failure of at least two different multidrug regimens. Their two most recent test results while on therapy must have shown a CD4 cell count below 100 cells/mm³ and a viral load above 5,000 copies/mL, or a CD4 cell count below 200 cells/mm³ and a viral load above 10,000 copies/mL. Exclusion criteria include currently taking a regimen of five or more anti-HIV drugs, inability to tolerate multiple drugs, or current serious OIs. Women may not be pregnant or breast-feeding.

In the U.S., the study will be conducted at 30 Veterans Administration medical centers, including Baltimore (410-605-7199), Boston (617-232-9500 ext. 4669), Cleveland (216-791-3800 ext. 4788), Dallas (214-857-0410), Durham (919-286-0411 ext. 7308), Los Angeles (310-268-3015), Miami (305-324-4455 ext. 4800), New York City (212-951-3348), Palo Alto (650-493-5000 ext. 63408), Philadelphia (215-823-5847), Phoenix (602-277-5551 ext. 6796), Portland (503-220-8262 ext. 57140), and San Diego (858-552-8585 ext. 2626). (CTN 167)

Therapeutic Drug Monitoring

This study will examine whether increased doses of PIs are more effective than standard doses. It will also look at the benefits of using therapeutic drug monitoring (TDM, or measuring drug levels in individuals) and drug resistance testing to guide drug selection and dose adjustment. Participants who have experienced treatment failure on their second, third, or fourth HAART regimen will receive drug resistance testing while still taking their failing therapy. At study entry subjects will begin a salvage regimen using drugs selected by their own physicians based on the results of the resistance tests. Two weeks later blood will be drawn to assess drug levels, and a “normalized inhibitory quotient” (NIQ) will be calculated for each subject. Those with an NIQ of 1 or less will be randomized to receive either standard antiretroviral therapy (arm A) or adjusted doses of PIs based on TDM test results

(arm B). Those with an NIQ greater than 1 will be randomized either to an observational arm (arm C) or to discontinue the study. Subjects in any arm who experience virological failure after the first week will be eligible to receive a second resistance test.

Participants must be at least 18 years of age and have a viral load of 2,000 copies/mL or more at study screening and at least one viral load measurement of 400 copies/mL or more within 60 days of study entry. Subjects’ failing HAART regimens must consist of at least three but fewer than six drugs; at least one failing regimen must have included a PI. Participants must have been taking their current regimen for at least 12 weeks before study entry. Exclusion criteria include having an acute illness requiring treatment within 21 days of study entry, cancer requiring radiation or chemotherapy, or a history of pancreas problems. Subjects should not have recently received experimental drugs, immune-modulating drugs, or HIV vaccines, and may not have used a previous mega-HAART regimen containing more than six drugs. Women must not be pregnant or breast-feeding.

Study sites include Boston (617-632-0785), Chicago (312-572-4545), Denver (303-372-5535), New York City (212-263-6565), Pittsburgh (412-647-0771), Rochester (585-275-2740), San Francisco (415-514-0550 ext. 362), and Seattle (206-731-8877). (ACTG A5146).

Interrupted vs Continuous Treatment

This randomized study will examine the benefits of short cycles of intermittent HAART vs continuous treatment. It will attempt to determine whether intermittent treatment suppresses viral replication and reduces drug side effects. Participants in one study arm will continue to receive their current HAART regimen on an ongoing basis, while those in the other arm will stop treatment every other week (seven days on followed by seven days off therapy) for 72 weeks. Blood will be drawn at the end of off-treatment cycles every month, or else every other month.

Participants must be at least 18 years of age and have been taking anti-HIV therapy (at least two NRTIs plus either an NNRTI or a PI) with an undetectable viral load for at least one month. They must have a CD4 cell count of at least 175 cells/mm³ within 30 days of study entry. Viral load must have been below 500 copies/mL for at least one month, and below 50 copies/mL at least once within 30 days of enrollment. Exclusion criteria include evidence of drug-resistant HIV, symptomatic OIs, hepatitis B, or serious conditions such as heart or kidney disease. Subjects may not be taking nevirapine (Viramune) or abacavir (Ziagen). Women must not be pregnant.

For more information and a list of study sites contact Diane Rock Kress, RN, at 301-435-8003 or 800-772-5464 ext. 58003. (M77-02-I-0013)

SMART: Drug Conservation vs Viral Suppression

The SMART study is a large trial comparing two HIV treatment strategies to determine whether participants at low risk of disease progression can safely reduce their use of anti-HIV therapy, thus staving off drug resistance and conserving treatment options until they are most needed. The drug conservation strategy involves episodic use of antiretroviral treatment for the minimum time necessary to maintain a CD4 cell count of at least 250 cells/mm³. The viral suppression strategy will attempt to keep viral load at undetectable levels regardless of CD4 cell count. Participants will be seen at months 1, 2, 4, 6, 8, 10, and 12 after study entry, and then every four months thereafter. For those in the drug conservation arm, treatment will be stopped upon enrollment. Therapy will be restarted (or started for the first time) if the CD4 cell count falls below 250 cells/mm³ and will be continued until there are two consecutive CD4 cell count measurements above 350 cells/mm³. For those in the viral suppression arm, current treatment will be continued (or treatment will be initiated) and modified as necessary to keep viral load as low as possible. Some 6,000 participants will be followed for an estimated 6–9 years, until 910 primary events (disease progression or death) occur. Selected groups of participants will be followed with more intensive data collection for secondary outcomes related to cost, health-care utilization, metabolic complications of treatment, and quality of life.

Participants must be at least 13 years of age and have a CD4 cell count above 350 cells/mm³. Subjects may be using any available antiretroviral and immune-modulating drugs at study entry. Women must not be pregnant or breast-feeding.

There are 20 study sites, including Boston (617-778-5456), Chicago (773-244-5802), Denver (303-436-7195), Fort Lauderdale (954-467-3006 ext. 223), Los Angeles (310-478-3711 ext. 40272), Minneapolis (612-347-7678), New Orleans (504-584-1971), New York City (212-939-2917), San Francisco (415-476-9554 ext. 23), and Washington, DC (202-745-8301). (CPCRA 065)

Shortstop: Resistance Testing

This study will evaluate the effectiveness of resistance tests in assessing whether specific drugs in an antiretroviral regimen are active against HIV. The trial is for people who have a detectable viral load despite treatment with d4T (stavudine, Zerit), ddI (didanosine, Videx), or efavirenz (Sustiva). Subjects will discontinue one of these drugs for two (d4T or ddI) or three (efavirenz) weeks, then the drug will be restarted. Blood will be drawn several times for viral load and genotypic and phenotypic resistance tests before, during, and after the discontinuation.

Participants must be at least 18 years of age, have a viral load between 5,000 and 100,000 copies/mL within six

weeks prior to prestudy screening, and have a CD4 cell count above 50 cells/mm³ within four weeks of enrollment or above 100 cells/mm³ within eight weeks of enrollment. They must have been on stable anti-HIV therapy containing d4T, ddI, or efavirenz for at least six months. Subjects must not have had an acute infection or received a vaccine within the previous four weeks. Certain anti-HIV and other drugs are excluded. Women may not be pregnant.

For more information and study sites, contact 800-772-5464 ext. 57689 or 800-411-1222. (01-I-0004)

ESPRIT: Interleukin 2

This randomized, open-label trial will evaluate the benefits of subcutaneous interleukin 2 (IL-2, Proleukin) in people receiving antiretroviral therapy. IL-2 is a protein produced by certain white blood cells that stimulates the production of CD4 cells. Past studies have shown that IL-2 can increase CD4 cell counts in people with HIV, but it is not clear whether this has any clinical or survival benefit. The goal of this trial is to determine the effect of IL-2 therapy on the rates of AIDS-related illness and death. Participants will be randomly assigned to receive IL-2 or no IL-2 (there is no placebo). Those receiving IL-2 will have twice-daily injections for five-day cycles every eight weeks. Clinic visits will take place at least every four months. The study is expected to last five years.

Participants must be at least 18 years of age and have a CD4 cell count of at least 300 cells/mm³. They must currently be taking anti-HIV therapy or be willing to start treatment. Exclusion criteria include any AIDS-defining illness in the past year, or current cancer or major heart, lung, kidney, central nervous system, or immune system disorders. Participants must not have taken IL-2 in the past, or corticosteroids or other immune-suppressing drugs or cytotoxic (cell-killing) agents within 45 days of study entry. Women must not be pregnant or breast-feeding.

There are over 30 study sites, including Atlanta (404-321-6111 ext. 3298), Berkeley (415-476-9554 ext. 22), Bethesda (301-435-7689), Detroit (313-343-7351), Houston (713-500-6751), Los Angeles (310-478-3711 ext. 42745), Miami (305-323-3267), Newark (973-483-3444 ext. 33), and San Francisco (415-476-9554 ext. 22).

Side Effects

Fat Irregularities and High Insulin Levels: Metformin and Rosiglitazone

This randomized, double-blind, placebo-controlled trial will evaluate the effect of metformin (Glucophage) and rosiglitazone (Avandia), taken alone or in combination, on high insulin levels and fat accumulation in the abdomen and other areas of the body. Metformin and rosiglitazone are currently approved by the Food and Drug Administration (FDA) for these indications in people without HIV. High

insulin levels and intra-abdominal obesity, both symptoms of HIV-related lipodystrophy syndrome, are risk factors for heart disease.

Several clinical measurements will be performed at study entry. Participants will be randomized to receive either metformin plus rosiglitazone placebo (arm A), rosiglitazone plus metformin placebo (arm B), metformin plus rosiglitazone (arm C), or placebos of both drugs (arm D). 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. Insulin and glucose levels will be assessed; blood must be drawn after fasting overnight. In addition, visceral (internal) fat, subcutaneous fat, and thigh size will be measured.

Participants must be between 18 and 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 have been taking a stable anti-HIV regimen for at least 60 days before study entry. Exclusion criteria include diarrhea, nausea, vomiting, or heart disease; previous use of drugs to control blood sugar; and use of immune-modulating drugs within six months of study entry. Participants may not be taking ritonavir with either simvastatin (Zocor) or lovastatin (Mevacor); there are also restrictions regarding use of hormones. Women must not be pregnant or breast-feeding.

Study sites include Birmingham (205-975-7925), Boston (617-726-3819), Chicago (312-695-5012), Cincinnati (513-584-8373), Honolulu (808-737-2751), Los Angeles (310-206-8029), New York City (212-420-4432), San Francisco (415-514-0550 ext. 362), and Washington, DC (202-687-5378). (ACTG A5082)

Women

Human Papillomavirus

This observational study will attempt to determine whether use of antiretroviral therapy affects the incidence of human papillomavirus (HPV) infection in women with HIV. HPV is associated with cervical, genital, and anal dysplasia (abnormal cell growth) and cancer. Researchers hypothesize that as anti-HIV treatment improves immune system function, women may be less likely to contract HPV or may experience less aggressive HPV disease. Participants will receive a pelvic exam and Pap smear at baseline, at weeks 24 and 48, and then every 48 weeks. Those with abnormal Pap smear results will receive a colposcopy (a procedure in which the cervix is examined with a lighted magnifying instrument). Blood will be collected to monitor HIV viral load, CD4 cell counts, and the presence of HPV antibodies.

Participants must be at least 13 years of age and intend to start antiretroviral treatment within 14 days of study

entry, either as part of another clinical trial or under the care of their own physician. Exclusion criteria include previous use of antiretroviral therapy for more than 14 days, or use of certain immune-modulating, anti-HPV, or experimental drugs. Subjects may not have a history of cervical cancer and may not have participated in previous HPV trials.

Study sites include Baltimore (410-614-4487), Birmingham (205-975-7925), Boston (617-632-0785), Los Angeles (323-343-8283), Miami (305-243-2154), New York City (212-420-4432), San Francisco (415-514-0550 ext. 362), and San Juan (787-759-9595). (ACTG A5029)

Alternative Therapies

Peripheral Neuropathy: Medical Marijuana

This study will evaluate the short-term safety and efficacy of smoked marijuana to relieve pain related to peripheral neuropathy. The study will consist of four stages: a seven-day outpatient period during which pain will be measured, a two-day inpatient lead-in stage, a seven-day inpatient intervention stage during which participants will smoke marijuana cigarettes three times per day, and a seven-day outpatient follow-up stage. A heat/capsaicin (hot pepper) pain test will be administered on days 1 and 7. Participants who complete all study stages will receive \$600.

Participants must be at least 18 years of age, have HIV-related painful neuropathy, have been taking stable anti-HIV therapy for the past eight weeks, and have used marijuana at least six times in the past. There are no CD4 cell count or viral load requirements. Exclusion criteria include use of smoked marijuana within 30 days of study entry; current tobacco smoking; active substance abuse; history of heart, lung, kidney, or liver disease; and active OIs requiring treatment. Women must not be pregnant or breast-feeding.

The study will take place in San Francisco (415-476-9554 ext. 21). (00018269)

Liz Highleyman (liz@black-rose.com) is a freelance medical writer and editor based in San Francisco.

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

glossary

A

ACTIVITY:

the immediate effect of a drug on a disease-causing microbe (pathogen). Contrast with *efficacy*.

ACUTE:

rapid in onset, aggressive; short-term initial stage of a disease. Contrast with *chronic*.

ANTIBODY (AB, IMMUNOGLOBULIN):

a protein secreted by activated plasma cells, which evolve from B cells. Antibodies are produced in response to stimulation by foreign antigens as part of the body's defense against invaders. Specific antibodies bind to and act upon specific antigens; the antigen-antibody reaction forms the basis of humoral (TH2) immunity.

ANTIGEN:

any agent or substance that stimulates an immune response. Antigens may be foreign microorganisms such as bacteria or viruses, or the substances they produce.

ANTIRETROVIRAL:

an agent (e.g., AZT, zidovudine, efavirenz) that suppresses the activity or replication of retroviruses such as HIV by interfering with various stages of the virus' lifecycle.

ARM:

a group of participants in a clinical trial who receive the same treatment (treatment arm) or placebo (control arm).

ASSAY:

a test, especially one used to detect the presence and/or concentration of a component, drug, or microorganism in the blood or other body fluids or tissues.

ASYMPTOMATIC:

not showing outward signs of a disease.

B

BASELINE:

an initial or known value (e.g., CD4 cell count, HIV viral load) against which later measurements can be compared.

C

CARDIOVASCULAR:

relating to the circulatory system (the heart and blood vessels).

CD4 CELL (CD4 LYMPHOCYTE, T-HELPER CELL):

a type of white blood cell that bears the CD4 surface receptor and helps the body fight infection. HIV attacks CD4 cells, typically resulting in their dysfunction or death.

CELL LINE:

a specific type of cell that is maintained in a laboratory for medical and/or research purposes.

CERVIX (*adjective* CERVICAL):

the cylindrical, lower part of the uterus leading into the vagina.

CHEMOTHERAPY (*adjective* CHEMOTHERAPEUTIC):

the use of chemicals or drugs to treat disease; the term is typically used to refer to cancer treatment.

CHOLESTEROL:

a fatty substance in animal tissue that is an essential component of cell membranes and nerve fiber insulation. There are two primary types of cholesterol in the blood: low-density lipoprotein (LDL), which is considered a risk factor for heart disease, and high-density lipoprotein (HDL), which is considered protective against heart disease.

CHRONIC:

persisting over a long period of time or recurring frequently. Contrast with *acute*.

CIRRHOSIS:

a condition in which the liver becomes scarred and fibrous, thus reducing its ability to function.

CLINICAL:

relating to the treatment of patients. A clinical observation is based on the observed condition of patients and their symptoms, as distinguished from blood tests or other laboratory findings.

COHORT:

a group of individuals in a study who share a demographic, clinical, or other characteristic (e.g., age, study site).

CYTOKINE:

an intercellular hormone or chemical messenger protein (e.g., tumor necrosis factor, interleukin) released by white blood cells (e.g., macrophages, T cells). Cytokines facilitate communication among immune system cells and between immune system cells and the rest of the body.

CYTOMEGALOVIRUS (CMV):

a herpesvirus that typically occurs in healthy individuals without causing symptoms. In immunocompromised individuals (usually those with fewer than 50 CD4 cells/mm³), CMV may cause serious illness including retinitis (inflammation of the retina), pneumonia, colitis (inflammation of the large bowel), and encephalitis (inflammation of the brain).

CYTOTOXIC T LYMPHOCYTE (CTL, KILLER T CELL):

a type of white blood cell that bears the CD8 surface receptor, and targets and kills cells infected with viruses, bacteria, or other microorganisms. The action of CTLs is coordinated by CD4 cells via the production of cytokines.

D**DEXA SCAN:**

dual energy x-ray absorptiometry, a method of determining the composition of body tissues.

DIURETIC:

an agent that increases the amount of urine excreted.

E**EFFICACY:**

effectiveness; the ability to achieve a desired effect, usually a drug's ability to control or cure an illness. Contrast with *activity*.

ENVELOPE (COAT):

the outer covering of some viruses. The HIV envelope contains spikes and is composed of two protein subunits—gp120 and gp41—encoded by the *env* gene.

ERADICATION:

the complete elimination of a microorganism (e.g., HIV) from the body, including the blood and reservoir tissue sites.

EXPANDED ACCESS:

an FDA program that allows distribution of experimental drugs through physicians to people with a life-threatening illness who have failed or cannot tolerate approved therapies, are unable to participate in clinical trials, and have no other treatment options.

F**FIRST-LINE THERAPY:**

the preferred, standard treatment for a particular condition.

G**GASTROINTESTINAL:**

relating to the stomach and intestines.

GENE (adjective GENETIC):

the unit of heredity. A gene contains hereditary information encoded in the form of DNA and is located at a specific position on a chromosome in a cell's nucleus. Genes determine many aspects of anatomy and physiology by controlling the production of proteins. Each individual has a unique sequence of genes, or genetic code.

GENOTYPE (adjective GENOTYPIC):

the specific genetic makeup or "blueprint" of an individual organism. Genotypic resistance testing determines whether HIV's genetic structure contains certain mutations that make it resistant to a drug. Contrast with *phenotype*.

GLUCOSE (BLOOD SUGAR):

a form of sugar that is the body's primary fuel; glucose broken down from food can be converted into energy or stored. Abnormally low or high levels of glucose in the blood often indicate metabolic disturbances (e.g., diabetes).

H**HAART:**

highly active antiretroviral therapy, a term for potent combination anti-HIV treatment that usually includes a protease inhibitor.

HEPATITIS B (HBV, SERUM HEPATITIS):

an infectious viral disease of the liver that may be acute or chronic. Chronic hepatitis B can lead to liver damage, cirrhosis, and/or cancer. HBV is a blood-borne virus that may be transmitted through shared needles, sexual contact, or from mother to infant.

HEPATITIS C (HCV, formerly NON-A, NON-B HEPATITIS):

an infectious viral disease that causes inflammation of the liver. Some individuals develop chronic hepatitis C, which can lead to life-threatening liver damage, cirrhosis, and/or cancer. HCV is a blood-borne virus that is spread, for example, through shared needles.

HYPERSENSITIVITY:

abnormal sensitivity; an exaggerated immune response to a substance such as an antigen or a drug.

I**IMMUNODEFICIENCY:**

inability of the immune system to work properly, resulting in susceptibility to disease. Immunodeficiency may be either congenital (present from birth) or acquired. HIV leads to immunodeficiency by attacking T cells.

IMMUNOSUPPRESSION (IMMUNOCOMPROMISE):

reduced function of the immune system; a state in which immune system defenses have been suppressed, damaged, or weakened.

INCIDENCE (INCIDENCE RATE):

the number of new cases of a disease or condition in a specific population during a given period of time. The incidence rate is determined by dividing the number of new cases by the total population. Contrast with *prevalence*.

INSULIN:

a hormone produced by the pancreas. Insulin enables the body to metabolize and use glucose. Lack of or insensitivity to insulin can result in diabetes.

INTERFERON:

one of a family of cytokines (messenger proteins) that play a role in immune response. Interferons are secreted by infected cells, and help protect other cells from infection.

IN VITRO:

Latin for “in glass.” Refers to studies done in a test tube or culture medium in the laboratory.

ISOLATE:

a specific individual microbe and its genetically identical progeny; a specific strain of HIV from a cultured cell line (laboratory isolate) or human (primary isolate).

L**LATE-STAGE DISEASE:**

advanced progression of a disease. Late-stage HIV disease, which typically occurs years or decades after initial infection, is characterized by low CD4 cell counts, high viral loads, wasting syndrome, and possibly opportunistic illnesses.

LIPID:

a fat.

LIPODYSTROPHY:

body fat irregularities, which may include wasting and localized fat accumulation. Also refers to a broader, poorly defined syndrome that may include altered fat metabolism, insulin resistance, and other manifestations.

LOG:

a measure based on the logarithmic scale that refers to quantities in factors of 10. A log change is an exponential or 10-fold increase or decrease (e.g., a change from 10 to 100 is a 1 log increase; 1,000,000 to 10,000 is a 2 log decrease). Changes in viral load are often expressed in logs.

M**MEAN:**

a statistical measurement of the central tendency, or average, of a set of values. Contrast with *median*.

MEDIAN:

the number within a series that is preceded and followed by an equal number of values; the middle value in a distribution, on either side of which lie an equal number of values. Contrast with *mean*.

METABOLISM (adjective METABOLIC):

the processes of building the body's molecular structures from nutrients and breaking them down for energy. Also, the chemical breakdown of drugs and toxins within the body.

MONOTHERAPY:

use of a single drug or other therapy.

MULTIVARIATE ANALYSIS:

a statistical analysis technique in which multiple variables are analyzed simultaneously, with correction for confounding associations, to determine the contribution made by each variable to an observed result.

MUTATION:

a change in the character of a gene that is perpetuated when a cell divides or a virus replicates. A mutant is a new strain of an organism produced by a genetic mutation.

N**NATURAL KILLER CELL (NK CELL):**

a type of white blood cell that attacks and kills tumor cells and cells infected with microorganisms. Unlike cytotoxic T lymphocytes, NK cells are nonspecific and attack infected cells without regard to specific antigens or MHC receptor configurations.

O**OPPORTUNISTIC ILLNESS (OPPORTUNISTIC INFECTION, OI):**

a condition that normally does not cause symptomatic illness in a person with a healthy immune system, but that may result in serious disease when the immune system is weakened. OIs in HIV positive people include infectious diseases such as *Pneumocystis carinii* pneumonia (PCP), *Mycobacterium avium* complex (MAC), and cytomegalovirus (CMV) infection, as well as cancers such as lymphoma.

P**PAP SMEAR (PAPANICOLAOU SMEAR):**

a procedure in which a specimen of cells is taken from the uterine cervix or anus, prepared on a slide, and examined under a microscope for abnormal cell growth. An abnormal Pap smear suggests increased risk of developing cancer.

PATHOGEN (adjective PATHOGENIC):

any disease-causing agent, especially a microorganism.

PHENOTYPE (adjective PHENOTYPIC):

visible characteristics and/or behavior that result from the interaction of an organism's genetic “blueprint” (genotype) and the environment. Phenotypic resistance testing determines whether HIV is susceptible to a specific drug in a test tube. Contrast with *genotype*.

PLACEBO:

an inactive substance (e.g., a “sugar pill”) or mock therapy. Experimental therapies are compared with placebos in many clinical trials.

PLASMA:

the yellowish, noncellular fluid component of circulating blood that carries blood cells and nutrients throughout the body, removes metabolic wastes, and is a medium for chemical communications between different parts of the body.

POSTEXPOSURE PROPHYLAXIS (PEP):

drug therapy given immediately following exposure to an infectious microorganism in an attempt to prevent the infection from taking hold in the body.

PREVALENCE (PREVALENCE RATE):

the number of existing cases of a disease or condition in a specific population during a given period of time. The prevalence rate is determined by dividing the number of people with the condition by the total population. Contrast with *incidence*.

PRODRUG:

an inactive form of a drug that exerts its effects after metabolic processes within the body convert it to a usable or active form.

PROGRESSION:

advancement or worsening of a disease.

PULMONARY:

relating to the lungs.

S**STANDARD OF CARE:**

the level of care that all persons with a particular illness should receive; the level below which care would be considered substandard.

STRUCTURED TREATMENT INTERRUPTION (STI):

starting and stopping treatment on a specified, monitored schedule.

SUBCUTANEOUS:

beneath the skin; subdermal.

SURROGATE MARKER:

a marker or sign that can serve in place of a clinical endpoint such as disease progression or death. Surrogate markers for HIV disease may be virological (e.g., viral load), immunological (e.g., CD4 cell count), or clinical (e.g., weight loss).

SYMPTOMATIC:

showing outward signs of a disease.

SYNERGY (SYNERGISM, *adjective* SYNERGISTIC):

an interaction between agents (e.g., drugs) that produces an effect greater than the combined effects of the same agents used separately.

T**T CELL (T LYMPHOCYTE):**

a type of white blood cell that matures in the thymus gland and carries out the cell-mediated immune response. There are three major types of T cells: CD4 helper T cells, CD8 suppressor T cells, and CD8 killer T cells (cytotoxic T lymphocytes or CTLs).

TRIGLYCERIDE:

a combination of glycerol and fatty acid that circulates in the blood. Elevated triglyceride levels, particularly when accompanied by elevated levels of low-density lipoprotein cholesterol, have been correlated with the development of cardiovascular disease.

V**VIRAL REBOUND:**

an increase in viral load following a previous decrease due to anti-HIV therapy.

VIRAL TURNOVER:

the rate at which virus dies and is regenerated.

VIRUS:

any of a large group of microorganisms that cannot grow or reproduce outside a host cell.

RESOURCES FOR THE DEAF AND THOSE WITH HIV-RELATED HEARING LOSS

- National AIDS Hotline**
 (Monday–Friday,
 10:00 AM to 10:00 PM, Eastern Time)
 800-243-7889 TTY
- National HIV/AIDS Treatment Information Service**
 (Monday–Friday,
 9:00 AM to 5:00 PM, Eastern Time)
 888-480-3739 TTY
www.hivatis.org
- Deaf AIDS Support Services (DASS) at the University of California, San Francisco (UCSF) Center on Deafness**
 415-476-7600 TTY
uccd@itsa.ucsf.edu
- Deaf AIDS Project (Baltimore, MD)**
 410-889-8077 TTY
www.deafvision.net/dap
- AIDS Initiative for Deaf Services Task Force (Hartford, CT)**
 860-951-4791 TTY
www.aidsprojecthartford.org/deafaidsct.html

AIDS Drug Assistance Programs (ADAP) by State

State	Telephone	State	Telephone
Alabama	.800-228-0469	Nebraska	.402-471-0362
Alaska	.907-263-2050	Nevada	.775-684-5952
Arizona	.602-230-5838	New Hampshire	.603-271-4480
Arkansas	.501-661-2466	New Jersey	.609-984-6328
California	.888-311-7632	New Mexico	.505-476-2363
Colorado	.800-858-2437	New York	.518-459-1641
Connecticut	.800-238-2503	North Carolina	.919-715-3118
Dist. of Columbia	.202-727-2500 ext. 9604	North Dakota	.701-328-4555
Delaware	.302-739-3032	Ohio	.614-466-8369
Florida	.850-245-4335	Oklahoma	.405-271-4636
Georgia	.404-657-3127	Oregon	.503-731-4029
Hawaii	.808-732-0026	Pennsylvania	.717-772-6057
Idaho	.208-334-6657	Puerto Rico	.787-763-4575
Illinois	.800-825-3518	Rhode Island	.401-277-2320 ext. 107
Indiana	.317-233-7450	South Carolina	.803-898-0705
Iowa	.515-242-5838	South Dakota	.605-773-3523
Kansas	.785-296-6036	Tennessee	.512-490-2500 ext. 2601
Kentucky	.502-564-6539	Texas	.800-255-1090
Louisiana	.504-568-7474	Utah	.801-538-6197
Maine	.207-287-5551	Vermont	.802-863-7253
Maryland	.410-767-5685	Virginia	.804-225-4844
Massachusetts	.617-624-5328	Washington	.360-236-3438
Michigan	.517-335-9333	West Virginia	.304-558-2958
Minnesota	.651-297-3344	Wisconsin	.608-266-0749
Mississippi	.601-576-7723	Wyoming	.307-777-5932
Missouri	.573-751-6439		
Montana	.406-444-4744		

AIDS/LifeCycle



Join us for an experience you'll remember for a lifetime.

San Francisco to Los Angeles. 585 Miles. June 8-14, 2003



AIDS/LifeCycle 2.

The second annual AIDS/LifeCycle promises to be a week full of fun, friends, magnificent scenery and thoughts of those for whom we ride. This 7-day cycling event will take you through some of California's most beautiful scenery—areas you may never have seen before, or at least not seen in this way—while camping along the way. And we'll raise millions of dollars that will make an extraordinary difference in the fight against the human suffering caused by AIDS.



AIDS Is Far From Over.

In California alone, there are more than 47,000 people living with AIDS* and another estimated 130,000 living with HIV.** And new infections are once again on the rise, with more than half occurring in communities of color and people under the age of 25. While advances in treatment for those living with HIV and AIDS have enabled them to live longer, this means that there is a greater need for services than ever before.

Proceeds from AIDS/LifeCycle will benefit the L.A. Gay & Lesbian Center and the San Francisco AIDS Foundation, two of the oldest and largest AIDS service organizations in the state that annually provide tens of thousands of people with medical care, counseling, housing and vital educational and preventative programs. Because the beneficiaries have assumed full responsibility for the production of AIDS/LifeCycle, you can be assured that costs will remain under control, thereby maximizing the return of funds for vital AIDS services.

The Event Experience.

While covering 585 scenic miles, you will encounter some long and winding roads that take your breath away.

And if you're worried about catching your breath afterwards, don't be. You'll ride at your own pace, even if that means riding in one of the support vehicles that will be along the route.

During the week of the event, we'll support you all the way. You'll get great food. Hot showers. Medical support. Luggage transport. Bike

maintenance. Tents. Road crews to guide and watch out for you. Rest stops, entertainment, massage therapy, and much more. Everyone on the AIDS/LifeCycle staff is with you 100% of the way to make sure your experience is extraordinary.

Our Support For You.

AIDS/LifeCycle is for everybody, which means no experience is necessary. We'll show you how to prepare nutritionally and physically—including a series of volunteer-led training rides in your area. You'll also be supported by your designated Cycle Buddy—someone on the AIDS/LifeCycle staff you can call for advice, tips on training, fundraising, or just for a motivational chat. And your AIDS/LifeCycle Manual will tell you all you need to know to get you from the first day of training to the final day of the event.

You'll need to raise a minimum of \$2500 in pledges. But this isn't as daunting as it sounds. Again, we'll be there to help with tips on finding sponsors, setting goals and getting big donations in small installments.

Your Cycle Buddy will work with you on a fundraising plan to meet your own personal objectives. And AIDS/LifeCycle will work hard to ensure that the maximum return for each dollar raised will support critical HIV/AIDS services.

Register Today.

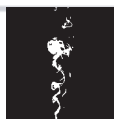
Register by calling **1-877-BIKE-4-AIDS**, or go to our official website at www.aidslifecycle.org to register online.

We can register you over the phone, or we can put a registration form and brochure in the mail to you right away. The AIDS/LifeCycle staff is standing by to help you with your fundraising and training.



REGISTER TODAY

1-866-BIKE-4-AIDS www.aidslifecycle.org



AIDS/LifeCycle™ is the official cycling event in support of the San Francisco AIDS Foundation and the HIV/AIDS services of the L.A. Gay & Lesbian Center
*CA Department of Health Services, Office of AIDS **Consensus meetings on HIV/AIDS Incidence and Prevalence in California, December 2001





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- ☺ Roche
- ☺ GlaxoSmithKline

and through the generous contributions of the many individual and institutional donors who support the San Francisco AIDS Foundation.