

Bulletin of Experimental Treatments for AIDS

BETA

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**Neurological
Complications**

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**A New Definition
of AIDS?**



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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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Liz
Highleyman

C O N F E R E N C E C O V E R A G E

Two major conferences addressing HIV/AIDS have taken place since the last issue of BETA, along with smaller meetings including the XIII International HIV Drug Resistance Workshop and the 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV.

XV INTERNATIONAL AIDS CONFERENCE

The XV International AIDS Conference, held July 11–16 in Bangkok, Thailand, drew some 20,000 participants. The conference was opened by United Nations Secretary-General Kofi Annan, and former South African president Nelson Mandela gave the closing address. As has become typical of the huge biannual conference, this year's event focused on political issues, including treatment access for developing countries (and the need for wealthy countries to contribute more to such efforts), gender inequality, epidemiology, and prevention issues (including vaccine and microbicide development).

Although access to treatment still lags in many developing countries, evidence continues to accumulate that antiretroviral therapy can be effective in such settings if the drugs are available. For example, the humanitarian group Médecins Sans Frontières (Doctors Without Borders) presented data from an analysis of more than 30 free antiretroviral treatment programs in Africa, Asia, and Latin America, which serve a total of more than 12,000 people. Use of antiretroviral therapy improved immune function and survival, even among individuals who started with low CD4 cell counts and advanced (WHO stage 4) HIV disease. Médecins Sans Frontières also reported that generic fixed-dose combination pills were as effective as the original brand-name drugs (although several generic drugs from India have since been taken off the WHO list of approved agents due to manufacturing irregularities). Other studies presented at the conference suggested that with appropriate support and education, people in resource-poor settings can adhere to anti-HIV therapy as well as those in the West.

2004 ICAAC

The 44th annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held October 30–November 3 in Washington, DC, drew a smaller crowd than the Bangkok conference and was more focused on basic and clinical science.

Treatment Regimens and Strategies

Many of the HIV presentations at ICAAC addressed specific antiretroviral regimens and treatment strategies.

Some HIV positive people and their physicians have sought to use regimens without protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs) in an attempt to avoid the side effects associated with these drug classes. Several past studies have suggested that regimens containing three nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are not sufficiently potent to suppress HIV, especially in people with high viral loads. But a study by Graham Moyle, MD, and colleagues (abstract H-1131) found that a regimen of four NRTIs—once-daily tenofovir DF (Viread) plus twice-daily Trizivir (AZT [zidovudine]/3TC [lamivudine]/abacavir combination pill)—was as effective and well tolerated as the NNRTI-based efavirenz (Sustiva, Stocrin) plus Combivir (AZT/3TC combination pill) regimen in treatment-naïve subjects. Edwin DeJesus, MD, and colleagues (abstract H-564) looked at an even simpler all-NRTI regimen—once-daily tenofovir plus once-daily Trizivir—but virological response was less impressive than that seen in Moyle's study, with several subjects developing resistance mutations after 24 weeks. Another presentation (abstract H-563) revealed that the tenofovir/Trizivir combination appeared effective in people who had experienced treatment failure with a prior NNRTI- or PI-based regimen.

In another attempt to avoid antiretroviral toxicity, many clinicians have come to favor NNRTIs over PIs for first-line therapy (see “In Their Own Words” on page 16). But according to a presentation by Pablo Barriero, MD (abstract H-576), individuals who interrupt or restart NNRTI-based regimens are more likely to develop drug resistance than those discontinuing PI-based therapy. It is well known that combination antiretroviral therapy generally produces the best outcomes, but two small studies add to the evidence that individuals on so-called Kaletra (lopinavir/ritonavir) monotherapy (in reality, two drugs) can maintain good viral control without developing resistance mutations (abstract H-183). While undetectable HIV RNA (viral load) remains the “holy grail” of antiretroviral

therapy, transient increases in viral load—often called blips—are common and do not appear to lead to the development of resistant virus, according to a presentation by Richard Nettles, MD (abstract H-1134).

Antiretroviral Side Effects

As has been the case at all recent HIV/AIDS conferences, side effects of antiretroviral therapy were a key topic at ICAAC. At the 11th Conference on Retroviruses and Opportunistic Infections in February 2004, researchers had reported that African Americans were more likely to experience side effects due to a genetic variation that slows clearance of efavirenz, leading to higher blood concentrations of the drug. A presentation at ICAAC showed that greater benefits accompany the increased risk. In a study by J. Guest and colleagues (abstract H-579), African Americans were less likely than white individuals to experience immunological failure (indicated by CD4 cell count increases of less than 50 cells/mm³) while taking efavirenz, although the risk of virological failure (indicated by continued detectable HIV viral load) did not differ among racial groups.

Research continues to accumulate that some PIs are better than others when it comes to metabolic side effects. A study by Mustafa Noor, MD, and colleagues (abstract H-162) confirmed past research showing that the newer PI atazanavir (Reyataz) was associated with fewer metabolic abnormalities than older drugs in its class. And the most recently approved PI, fosamprenavir (Lexiva), was linked to increased levels of HDL “good” cholesterol. According to a presentation (abstract H-156) by Jeffrey Nadler, MD, in the NEAT study, subjects receiving fosamprenavir experienced mean HDL increases of 37%, compared with 22% in those taking nelfinavir (Viracept); however, the ratio of total cholesterol to HDL was little changed.

Individuals who experience altered lipid profiles while taking HAART are often prescribed lipid-lowering drugs in an effort to reduce their cardiovascular risk. But according to a study by J. Bhalodia and colleagues (abstract H-155), such medications are not completely effective in reversing blood lipid changes associated with antiretroviral therapy.

Bone loss is another metabolic complication that has been linked to antiretroviral therapy and/or HIV infection itself. In a study of 267 HIV positive individuals (85% male, 61% African American, average age 41 years) Naomi Aronson, MD, and colleagues observed osteopenia (mild bone loss) in 40% and osteoporosis (more severe bone loss) in 6% of the subjects (abstract H-166). However, no significant association was detected between bone loss and use of d4T (stavudine, Zerit), tenofovir, or any PI.

New Anti-HIV Drugs

Like most major HIV/AIDS conferences, the 2004 ICAAC also featured several presentations on experimental antiretroviral agents. Robert Murphy, MD, presented final ten-week data (abstract H-1130) from a study of an investigational NRTI known as D-D4FC, or Reverset (for more on this agent, see “Drug Watch,” *BETA*, Summer 2004). In ten treatment-experienced subjects with various resistance mutations, HIV viral load decreased by a mean of 0.8 logs; in treatment-naive individuals, the corresponding decrease was 1.77 logs. (Log changes in viral load are used as scientific shorthand. A 0.3 log change is a two-fold change; a 0.5 log change, 66.6%; a 1 log change, 90%; and a 2 log change, 99%.)

In another study of 39 subjects, a new experimental NNRTI, GW695634, was well tolerated with no serious adverse side effects (abstract A-23). This compound, which has shown impressive anti-HIV activity in the laboratory, is now entering clinical trials to determine its efficacy in humans. Looking at a new class of anti-HIV drugs, Jay Lalezari, MD, presented data from a Phase I study of 837140, a new CCR5 antagonist entry inhibitor being developed by GlaxoSmithKline (abstract H-1137b). During

O N T H E W E B

XV INTERNATIONAL AIDS CONFERENCE:

www.aids2004.org

44TH ICAAC:

www.icaac.org/44ICAAC/44icaac.asp

FOR MORE COMPLETE COVERAGE OF THESE AND OTHER RECENT CONFERENCES, SEE:

www.aidsmap.org

www.hivandhepatitis.com/int_conf_rpt.html

www.natap.org

www.thebody.com/confs/confcov_recent.html

treatment with 837140, subjects experienced viral suppression in a dose-dependent manner, and no significant adverse side effects were reported.

GUIDELINES, DRUG APPROVALS, AND LABEL CHANGES

Revised Federal Treatment Guidelines

On October 29 the U.S. Department of Health and Human Services (DHHS) issued the latest revision of its *Guidelines for the Use of Antiretroviral Agents in HIV-1–Infected Adults and Adolescents*. The new version was rewritten to improve readability and contains a number of important changes, but no radical shifts in treatment philosophy. The DHHS panel of experts made changes concerning the role of HIV viral load in guiding treatment decisions. In a continuation of the trend away from the “hit hard, hit early” strategy and toward later therapy, the viral load cut-off for initiating HAART in asymptomatic, treatment-naive individuals was raised from 55,000 to 100,000 copies/mL (having previously been increased from 20,000 copies). The panel recommended that people with HIV RNA levels above 100,000 copies/mL should begin HAART even if their CD4 cell counts remain above 350 cells/mm³. Conversely, individuals with CD4 counts below 200 cells/mm³ are advised to begin treatment even if they have low viral loads.

The revised guidelines include an extended discussion of which antiretroviral regimens to use for first-line therapy, as well as interruption or discontinuation of treatment. Given the side effects associated with d4T, including lipodystrophy (fat loss in the face and limbs) and possible mitochondrial toxicity, this NRTI was demoted from a “preferred” to an “alternative” medication. Tenofovir and the recently approved FTC (emtricitabine, Emtriva) were included as components of a dual-NRTI “backbone” for use with either NNRTI- or PI-based regimens. Hydroxyurea (Hydrea) was deleted from the guidelines, since it is not an antiretroviral medication indicated for the treatment of HIV. The latest revision also adds information about treatment of special populations, including HIV positive adolescents, injection drug users, and HIV positive individuals coinfecting with hepatitis B or C, and/or tuberculosis. The revised DHHS guidelines can be viewed at www.aidsinfo.nih.gov/guidelines.

FDA Approves Two Fixed-Dose Combos

On August 2 the U.S. Food and Drug Administration (FDA) approved two new NRTI fixed-dose combination pills. Truvada, manufactured by Gilead Sciences, contains

200 mg FTC plus 300 mg tenofovir. For full prescribing information, see www.truvada.com. The new product was approved in just four months under the FDA’s recently implemented priority review process for fixed-dose combinations. Epzicom, produced by GlaxoSmithKline (GSK), combines 300 mg 3TC plus 600 mg abacavir. For full prescribing information, see www.epzicom.com. GSK also manufactures the two previously available fixed-dose anti-HIV combination pills, Combivir (AZT/3TC) and Trizivir (AZT/3TC/abacavir).

Fixed-dose combinations allow individuals to take fewer pills per day, potentially improving adherence. Truvada and Epzicom are the first once-daily fixed-dose combination pills. Combining the new pills with atazanavir or efavirenz allows for a complete once-daily regimen. To construct an effective anti-HIV regimen, Truvada and Epzicom should be used with a PI or an NNRTI, not alone or only with other NRTIs.

Truvada was approved largely on the basis of study data for a similar agent, 3TC. Soon after the combination pill was approved, Gilead released preliminary 24-week data from Study 934, a multicenter trial of 509 participants, showing that tenofovir/FTC works better than AZT/3TC when used in combination with efavirenz (these results were also presented as a late-breaker at ICAAC, abstract H-1137c). In this study, 88% in the tenofovir/FTC arm achieved viral loads below 400 copies/mL, compared with 80% in the AZT/3TC arm; discontinuation rates were 3% and 9%, respectively.

Truvada appears safe based on studies to date, but the tenofovir component has been associated with kidney problems in a small number of individuals. The abacavir in Epzicom can cause a potentially life-threatening allergic reaction in about 5–8% of people who use it. Anyone with known hypersensitivity to abacavir should not take Epzicom (or Trizivir). If such a reaction is suspected (symptoms may include skin rash, fever, nausea, abdominal pain, sore throat, cough, and/or shortness of breath), the drug should be stopped immediately and not restarted.

Both Epzicom and Truvada will sell for a wholesale price of about \$800 per month. GSK announced that it would issue a limited supply of vouchers for a free two-month supply of Epzicom to people who are starting anti-HIV treatment or who need to change their regimens; it will also provide the combination pill at a much lower no-profit price in developing countries. Gilead will offer Truvada to HIV positive people in the U.S. who are unable to afford or obtain reimbursement for the product; this company, too, will provide its new combination pill to 68 developing countries (mostly in Africa) at the no-profit price of about \$30 per month.

See page 48 for information on an open-label study of tipranavir currently enrolling at over 60 sites.

FDA Gives Final OK to Sculptra

The FDA announced in early August that it had granted approval for Sculptra (poly-L-lactic acid), a synthetic injectable polymer used to fill in sunken cheeks in people with HIV-related facial wasting, or lipoatrophy. Sculptra, manufactured by Dermik Laboratories, causes the body to produce collagen (a fibrous protein) to replace lost fat. As reported in the previous issue of *BETA*, an FDA advisory group recommended approval of Sculptra in March 2004. In four studies including a total of more than 250 participants (mostly white men), treated individuals reported good results, including improved appearance, reduced depression, and improved quality of life. As a condition of approval, the company agreed to conduct a post-marketing study that will include more women and people of color. Common side effects of Sculptra include pain, temporary bruising or swelling, and small nodules (lumps) under the skin; for optimal results, the product should be administered only by a trained practitioner. Because the substance is biodegradable, the therapy is not permanent and repeated injections may be necessary. Poly-L-lactic acid has been available for cosmetic use in Europe since 1999 under the name New-Fill. The recent U.S. approval covers only HIV-related facial fat loss, but the advisory panel expressed concern that once approved, the product could be used off-label for cosmetic purposes such as wrinkle reduction.

FDA Reviewing Once-Daily Kaletra, Approves New Invirase Pill

In July Abbott Laboratories submitted a supplemental new drug application (NDA) for a once-daily indication for its PI Kaletra (lopinavir boosted with ritonavir). The request is based on study data showing that once-daily and twice-daily Kaletra had similar efficacy when used in combination with FTC and tenofovir in treatment-naïve people (ICAAC abstract H-570). In October the Kaletra product label was revised to include new longer-term data from two trials showing that the drug was still effective after 144 and 204 weeks. The revision also included a caution regarding increased blood concentrations of the drug in people with liver impairment due to hepatitis C, as well as some additional drug interactions. The revised label may be viewed at www.kaletra.com.

In related news, the FDA announced in December that it had approved Roche's new 500 mg tablet of hard-gel saquinavir (Invirase). The new formulation is smaller than the existing 200 mg pill, and only two are taken at a time (previously, the approved dose was five 200 mg tablets twice daily). Invirase should be used only if boosted with

ritonavir (Norvir), which is necessary to enable optimal absorption (ICAAC abstract A-453).

Tipranavir Approval Requested

In late October Boehringer Ingelheim requested U.S. and European approval for tipranavir, its investigational nonpeptidic PI. The drug has been studied in treatment-experienced individuals as past research shows it works against HIV that has developed resistance to other drugs in its class. The NDA for tipranavir is based on data from two large Phase III trials, RESIST-1 and RESIST-2. At the 2004 ICAAC Charles Hicks, MD, presented interim data from RESIST-1 showing that twice-daily tipranavir boosted with ritonavir worked better than other ritonavir-boosted PIs (Kaletra, amprenavir [Agenerase], indinavir [Crixivan], or saquinavir [Invirase or Fortovase]) in subjects with PI-resistant HIV (late-breaker abstract H-1137). After 24 weeks, about 42% of subjects receiving tipranavir achieved at least a 90% decrease in viral load, compared with about 22% of those taking other PIs; in addition, about twice as many in the tipranavir arm achieved undetectable viral loads (below 400 copies/mL). Subjects receiving tipranavir were significantly more likely to experience severe (grade 3 or 4) ALT (liver enzyme) elevations than those taking other PIs (7% vs 1%, respectively). Some research suggests that tipranavir reduces blood levels of other PIs, which could make it unsuitable for use in salvage regimens that combine multiple PIs. Boehringer is seeking accelerated approval from the FDA, and asked for a priority six-month review; if granted, the company expects that the drug may be available as soon as the spring of 2005.

Meanwhile, a new expanded access program (EAP) for tipranavir started on November 30. The drug will be available through physicians for people with limited treatment options who need tipranavir to construct a viable anti-HIV regimen. Eligible individuals will have previously used at least two PI-based regimens and have documented PI resistance. There are no viral load or CD4 cell count restrictions. Individuals enrolled in ongoing clinical trials of tipranavir are not eligible for the EAP. Physicians may register to participate in the program at www.tpv-eap.com. For more information about the program, visit the web site or call 888-524-8675.

In response to the pending commercial availability of tipranavir, which requires a high 400 mg boosting dose of ritonavir, the latter drug's manufacturer, Abbott Laboratories, announced that it would expand its Patient Assistance Program to provide high-dose ritonavir for free. Abbott came under fire in December 2003 when it increased the price of ritonavir by 400%. Under the new expansion, everyone is eligible for free high-dose ritonavir, including people obtaining their medications through private insurance,

Medicaid/Medicare, or an AIDS Drug Assistance Program (ADAP). Physicians must request ritonavir for their patients. A lower dose of ritonavir (typically 100 mg) is used to boost several other PIs; people with private insurance or public benefits that cover the drug remain ineligible for free low-dose ritonavir. For more information, call 800-222-6885.

Priority Review for HIV/HCV Coinfection Treatment

The FDA announced in October that it would grant priority review status for Roche's Pegasys brand of pegylated interferon-alpha-2a plus ribavirin (Copegus) for the treatment of chronic hepatitis C virus (HCV) infection in individuals coinfecting with HIV. The combination, which is already standard therapy for people with hepatitis C alone, could be approved for coinfecting individuals by April 2005. The European Medicines Agency recommended approval of the regimen for this population this past December. As presented at the 2004 Retrovirus conference and reported in the previous issue of *BETA*, treatment with this combination in the APRICOT study yielded a sustained virological response (SVR) rate of 40% in coinfecting subjects (62% for HCV genotypes 2 or 3; 29% for genotype 1, which is most common in the U.S. and is most difficult to treat). SVR refers to continued undetectable HCV viral load six months after the end of treatment. In the ACTG A5071 study, presented at the same conference, the SVR rate for Pegasys plus ribavirin was 27% (73% for genotypes 2 or 3; 14% for genotype 1). Both studies were published in the July 29, 2004 issue of the *New England Journal of Medicine* (*NEJM*).

First Generic Antiretroviral Approved

On December 3 the FDA announced the approval of a generic formulation of delayed-release ddi (didanosine), which is sold by Bristol-Myers Squibb under the brand name Videx EC. This is the first time a generic anti-HIV medication has received approval in the U.S., although several generic antiretroviral drugs and fixed-dose combinations are available in other countries. The new generic ddi, manufactured by Barr Laboratories, will be available in 200 mg, 250 mg, and 400 mg capsules, and has the same indications as the brand-name version of the drug.

Amprenavir to Be Withdrawn from Market

GlaxoSmithKline announced in September that it would discontinue the sale of its PI amprenavir (Agenerase) by the end of 2004—the first approved antiretroviral drug to be taken off the market. The move is due to decreased demand for amprenavir following the approval of fosamprenavir (Lexiva), a prodrug of

amprenavir that reaches higher concentrations in the blood and allows users to take fewer pills. The latest revision of the federal HIV treatment guidelines includes fosamprenavir, but no longer amprenavir, as a preferred component of antiretroviral therapy.

Product Label Revisions

In July the FDA approved a new dosing regimen for atazanavir (Reyataz). For treatment-experienced individuals, the new recommended dose is 300 mg atazanavir (two 150 mg capsules) plus 100 mg ritonavir taken once daily with food. For treatment-naïve people, the dose is still 400 mg (two 200 mg capsules) atazanavir once daily with food. The revised recommendation is based on data from Study AI424-045 showing that the new atazanavir/ritonavir dosing regimen worked as well as twice-daily Kaletra. After 48 weeks of treatment, 55% in the atazanavir arm and 57% in the Kaletra arm had HIV viral loads below 400 copies/mL (38% and 45%, respectively, below 50 copies/mL). The revised product label, which also includes new information about the use of atazanavir in first-line regimens, is available at www.reyataz.com.

The following month, the product label for efavirenz (Sustiva, or Stocrin outside the U.S.) was revised to expand the indication to include long-term therapy. The change is based on new clinical trial data from Study 006 showing that efavirenz remains effective after more than three years. After 168 weeks, 48% of subjects receiving efavirenz/AZT/3TC, 40% of those taking efavirenz/indinavir, and 29% of those taking indinavir/AZT/3TC achieved viral loads below 400 copies/mL (43%, 31%, and 23%, respectively, below 50 copies/mL). The revised label, which also includes new information on psychiatric side effects, hepatotoxicity, and drug interactions, can be viewed at www.sustiva.com.

Finally, product labels for several antiretroviral drugs were revised to include information on immune reconstitution syndrome (IRIS). This condition occurs when effective antiretroviral therapy improves immune function enough to cause the immune system to mount an inflammatory response to indolent (subclinical) or residual (low-level) opportunistic pathogens such as *Mycobacterium avium*, *Mycobacterium tuberculosis*, *Pneumocystis carinii* (now called *P. jirovecii*), or cytomegalovirus (CMV). When this happens, opportunistic illness symptoms may temporarily arise or worsen, since some such symptoms are caused by the immune system's response to a pathogen, rather than as a direct effect of the pathogen itself. For more information on IRIS, see "Immune Reconstitution Syndrome" on page 12.

People with persistent, detectable but low-to-moderate viral load levels may continue to do well and are not necessarily at increased risk of HIV disease progression.

DRUG WARNINGS

Tenofovir in HIV/HBV-Coinfected Individuals

In July the tenofovir DF (Viread) product label was revised to add a “black box” warning that the drug is not indicated for the treatment of chronic hepatitis B virus (HBV) infection, and that it has not been shown to be safe or effective in HIV/HBV-coinfected individuals. Severe worsening of hepatitis B symptoms (“flares”) have been reported in coinfecting individuals who have stopped tenofovir. Such flares may also occur when stopping 3TC or FTC. It is recommended that HIV positive people be tested for HBV before starting antiretroviral therapy and have their liver function monitored for several months following discontinuation of tenofovir. Several studies have shown that tenofovir reduces HBV replication in coinfecting individuals, but this use is still considered experimental and research is ongoing. The revised label, which also includes new information about drug interactions with atazanavir and Kaletra, is available at www.viread.com.

Kaletra/Phenytoin Interaction

According to a report by Michael Lim, PharmD, and colleagues published in the August 15, 2004 issue of the *Journal of Acquired Immune Deficiency Syndromes (JAIDS)*, the anticonvulsant drug phenytoin (Dilantin) may reduce blood concentrations of Kaletra, while Kaletra appears to increase phenytoin levels. This occurs because both drugs are metabolized by the same cytochrome P450 (CYP450) enzymes in the liver. The combination should be avoided or used with caution, including drug level monitoring, to avoid subtherapeutic Kaletra levels and/or intensified phenytoin side effects.

Erythromycin/PI Coadministration Increases Heart Risk

The common oral antibiotic erythromycin can increase the risk of sudden cardiac death when administered concurrently with PIs and other medications metabolized by the same CYP450 system of liver enzymes, researchers reported in the September 9, 2004 issue of *NEJM*. Erythromycin can prolong heart repolarization, causing potentially fatal heart rhythm disturbances. In people taking other drugs metabolized by the same CYP3A liver enzyme, blood concentrations of erythromycin may be higher, thus increasing the risk of adverse cardiac events. Wayne Ray and colleagues examined the medical records of Tennessee Medicaid recipients covering 5,305 total person-years (PY) of erythromycin use; during this time there were ten cases of sudden cardiac death with no known cause, for a rate of 1.2 per 1,000 PY. However,

three such deaths occurred in people using erythromycin plus drugs metabolized by the CYP3A enzyme, for a sudden cardiac death rate of 15.5 per 1,000 PY in this subgroup. In a multivariate analysis, the adjusted rate of sudden cardiac death was twice as high among subjects using erythromycin, and five times as high among those using both erythromycin and CYP3A-inhibiting drugs. Although HIV positive individuals were not included in this analysis, PIs are known to be potent inhibitors of CYP3A activity. The researchers recommended that erythromycin not be used at the same time as CYP3A inhibitors.

Caution Regarding Tenofovir/ddI Combination

On November 12 Bristol-Myers Squibb issued a letter to health-care providers concerning data from two studies showing that use of tenofovir plus delayed-release ddI (Videx EC) plus either efavirenz or nevirapine (Viramune) led to virological failure in an unexpectedly high proportion of individuals. In one open-label study, six of 14 subjects using tenofovir/ddI/efavirenz experienced treatment failure, and a retrospective database analysis found that five of ten subjects on this regimen did not achieve HIV suppression. In another retrospective database analysis, two of four subjects receiving tenofovir/ddI/nevirapine experienced treatment failure. Virological failure tended to occur early and was most pronounced in people with high baseline viral loads. In October Gilead issued a warning letter regarding the high failure rate of tenofovir/ddI/3TC. While several triple-NRTI regimens have proven insufficiently potent, there has been concern about the tenofovir/ddI combination in particular. However, tenofovir/ddI has been shown to be effective in other studies, including one that found tenofovir/ddI to be a superior NRTI backbone in regimens containing boosted PIs. The company advised clinicians to exercise caution when administering tenofovir/ddI plus either efavirenz or nevirapine, and stated that further investigation is underway.

OTHER HIV/AIDS NEWS

Viral Load and CD4 Cell Count

Several recent studies have examined anti-HIV treatment strategies and their relation to viral load and CD4 cell count.

Stephen Raffanti, MD, and colleagues with the Collaborations in HIV Outcomes Research/U.S. study reported in the September 1, 2004 issue of *JAIDS* that people with persistent, detectable but low-to-moderate viral load levels may continue to do well and are not necessarily at increased risk of HIV disease progression. The researchers, following more than 3,000 subjects for up to 4.3 years, found that people with viral loads between 400 and 20,000

copies/mL were no more likely to develop AIDS-defining illnesses or to die than people with HIV RNA levels below the 400 copies/mL limit of detection. Those with viral loads above 20,000 copies/mL, however, had a significantly higher risk of disease progression and death. Although clinical outcomes were similar for people with 400–20,000 copies/mL and those with fewer than 400 copies/mL, the subjects who maintained lower viral loads experienced greater CD4 cell increases (75 vs 13 cells/mm³, respectively); subjects with more than 20,000 copies/mL lost an average of 23 cells/mm³. “These data suggest that maintenance of moderate viremia may confer clinical benefit not seen when viremia exceeds 20,000 copies/mL,” the authors concluded. “[T]his should be taken into account when considering the risks and benefits of continuing failing therapy.” These results do not change the optimal goal of achieving undetectable viral load; if it is possible to construct a more effective regimen, this should be done. However, the study does suggest that treatment-experienced individuals with limited remaining therapeutic options may benefit from staying on a “failing” regimen.

In the same issue, Colette Smith, MSc, and colleagues reported that viral load after four weeks of antiretroviral therapy could predict longer-term response. In their study, subjects who achieved a good early virological response were more likely to have undetectable HIV RNA at 24 weeks; 84% of subjects with fewer than 1,000 copies/mL, 61% of those with 1,001–10,000 copies/mL, 37% of those with 10,001–100,000 copies/mL, and 24% of those with more than 100,000 copies/mL at four weeks had HIV RNA levels below 50 copies/mL at week 24. The researchers calculated that for every 1 log change in viral load at four weeks, the odds of achieving an undetectable viral load at 24 weeks decreased by 65%. If treatment response after one month can be used to predict outcomes at six months, the four-week viral load measurement could help clinicians adjust therapy at an early stage in people who do not appear to be responding optimally, thus helping prevent the emergence of drug-resistant virus.

Finally, in the November 1, 2004 issue of the same journal, Daniel Skiest, MD, and colleagues reported that treatment interruptions appear safe for people who had nadir (lowest ever) CD4 cell counts above 350 cells/mm³ before starting antiretroviral therapy. The latest DHHS HIV treatment guidelines (see previous news item) recommend starting therapy when the CD4 cell count falls below 350 cells/mm³, but progression to AIDS is uncommon in people with counts above 200 CD4 cells/mm³. What to do if the CD4 count falls within the 200–350 cells/mm³ range remains uncertain. In Skiest’s study of 107 subjects, the

median CD4 cell count before starting therapy was 463 cells/mm³. After stopping HAART, CD4 counts declined by 8 cells/mm³ per month; viral load increased by about 2.54 log copies/mL during the first two months off therapy, but thereafter remained stable for the duration of the study. Subjects remained off therapy for a median of 8.9 months, and responded favorably when they restarted treatment. No AIDS-defining events were observed during ten months of follow-up. The results of this study suggest that people with nadir CD4 cell counts above 350 cells/mm³ may have started treatment “too soon,” and thus can safely stop therapy; it does not, however, imply that structured treatment interruptions in general are safe.

Should Injection Drug Users Start Treatment Earlier?

Injection drug users (IDUs) may benefit from earlier treatment than other people with HIV, suggests a study published in the September 15, 2004 issue of the *Journal of Infectious Diseases (JID)*. C. Cun-lin Wang and colleagues from the Baltimore-based AIDS Linked to Intravenous Experience (ALIVE) study analyzed data from 583 HIV positive and 920 HIV negative IDUs (about 75% male, 90% African American, median age about 42 years) between 1997 and 2000. The researchers found that during follow-up, the mortality rate from any cause was lowest among HIV negative IDUs (19.9 per 1,000 PY). Among HIV positive subjects, the all-cause mortality rate was 24.1 per 1,000 PY for those who started HAART with CD4 cell counts above 350 cells/mm³ (not significantly different from the rate in the HIV negative group), but 50.5 per 1,000 PY for those who started HAART with CD4 cell counts of 200–350 cells/mm³, and 86.7 per 1,000 PY for those who began treatment with CD4 cell counts below 200 cells/mm³.

Only IDUs who started therapy at CD4 cell levels above 350 cells/mm³ gained the full survival benefit from HAART. Looking at just AIDS-related mortality, the rates in HAART-treated and untreated IDUs were similar in those with more than 350 cells/mm³ or 200–350 cells/mm³; among those with fewer than 200 cells/mm³, however, HAART still conferred a significant survival benefit. Also, among individuals with 200–350 cells/mm³, higher viral loads were associated with poorer survival. The current DHHS guidelines (see previous news item) recommend initiating treatment when the CD4 cell count falls below 350 cells/mm³, although research suggests that most asymptomatic HIV positive people can safely wait until their CD4 cell counts approach 200 cells/mm³. But in IDUs, according to the authors, “to optimize survival...

initiation of HAART at CD4 cell levels higher than the current treatment guidelines indicate might be considered.”

Anti-HIV Effect of Statins

According to a study in the August 16, 2004 issue of the *Journal of Experimental Medicine*, drugs in the statin class (e.g., pravastatin [Pravachol], atorvastatin [Lipitor]), which are used to reduce elevated cholesterol levels, appear to have activity against HIV both in the laboratory and in humans. Gustavo del Real and colleagues from the Spanish Council for Scientific Research found that statins inhibited HIV infection of cells both *in vitro* and in mice, apparently by preventing the virus from crossing host cell membranes, a process that requires adequate cholesterol levels. Further, administration of the drug lovastatin (Mevacor) was associated with modestly decreased HIV viral loads and increased CD4 cell counts in a small study of six treatment-naïve HIV positive individuals (three of whom were coinfecting with hepatitis C); after the statin was discontinued, viral load rebound occurred. Although this research is only at the proof-of-concept stage, it suggests that the low-cost statins could potentially be used as a component of anti-HIV therapy.

Further Risks of Smoking

According to a study presented at the Bangkok AIDS conference and the 70th annual meeting of the American College of Chest Physicians, HIV positive smokers are more likely to develop chronic obstructive pulmonary disease (COPD) than their HIV negative counterparts. Kristina Crothers, MD, of Yale University School of Medicine and colleagues studied 895 HIV positive and 653 HIV negative veterans. In this cohort, HIV positive individuals with a total of 40 pack-years of smoking had 5.5 times the risk of COPD as HIV negative people who smoked the same amount. After adjusting for various risk factors such as age and smoking history, subjects with HIV were 59% more likely to develop COPD. Crothers did not have a clear explanation for the findings, but suggested that “HAART therapy or HIV itself may be factors promoting COPD.” She also found that HIV positive smokers tended to have higher viral loads than HIV positive nonsmokers, even though a similar percentage in both groups (90%) were on HAART. The smokers also reported lower quality of life scores and had a higher overall mortality rate. COPD is a progressive condition that is seen more often as people age; as people with HIV live longer, they are prone to this and other chronic problems associated with aging (see “Mortality Trends” on page 18). Clinicians should assess respiratory function in their HIV positive patients who exhibit persistent respiratory symptoms.

Uncommon Infection Seen in San Francisco, Europe

In late December the San Francisco Department of Public Health (SFDPH) announced that a rare sexually transmitted infection (STI), lymphogranuloma venereum (LGV), had been detected in four men who have sex with men in the city. LGV is caused by a strain of *Chlamydia trachomatis*, bacteria associated with the common STI chlamydia (chlamydia). While chlamydia often causes no symptoms or only mild genital discharge and/or pain, LGV may lead to genital and rectal ulcers, proctitis (rectal inflammation), constipation, flu-like symptoms, potentially severe gastrointestinal distress, and swollen lymph nodes (especially in the groin area). Although Dr. Sam Mitchell of the SFDPH said that HIV positive individuals are not known to be at higher risk for LGV, any STIs that cause open ulcers can increase the risk of HIV transmission.

LGV made the news earlier in 2004 when officials reported an outbreak of nearly 100 cases among gay and bisexual men in the Netherlands (an early cluster of 15 cases was reported in the October 1, 2004 issue of *Clinical Infectious Diseases*). Other isolated cases were detected in Britain, France, Belgium, and Sweden—countries where the disease is also rare. LGV is more typically seen in tropical developing countries in Africa, Latin America, the Caribbean, and Asia. None of the San Francisco men with LGV reported having recently visited the Netherlands, suggesting the possibility of multiple independent outbreaks. LGV can be treated and cured with a three-week course of doxycycline, although eradication is more likely with an early diagnosis. The SFDPH recommends that all cases of rectal chlamydia be presumptively treated as if they were LGV. The risk of LGV transmission can be reduced by using condoms for anal sex.

Syphilis and HIV

Researchers and public health officials have expressed increasing concern in recent years about high rates of syphilis in certain groups of men infected with or at risk for HIV. Research shows that syphilis increases the likelihood of HIV acquisition and transmission, and the disease is an indicator of unprotected sexual activity. According to a Chicago Department of Public Health (CDPH) study published in the October 22, 2004 issue of *Morbidity and Mortality Weekly Report*, the incidence of syphilis is on the rise, and the disease can be spread through oral as well as anal or vaginal sex. In the 1998–2002 period, the CDPH recorded 1,582 cases of primary or secondary syphilis, or 11–12 cases per 100,000 persons. During this interval, the majority of cases shifted from heterosexuals throughout most of the 1990s to men who have sex with men (MSM)

The “top” in anal sex may be at greater risk of HIV infection than previously believed.

since 2001. Case rates declined dramatically among women (from 9.2 to 2.9 per 100,000), but increased among men (from 14.7 to 22.1 per 100,000). While 90% of heterosexual cases occurred in black individuals, the racial breakdown among MSM was 54% white, 26% black, and 13% Latino. Less than 10% of the heterosexual cases, but about half the cases among MSM, were in HIV positive people. Based on interviews and surveillance data, Carol Ciesielski, MD, and colleagues estimated that nearly 14% of Chicago syphilis cases are attributable to oral sex—a rate that increases to just over 20% for gay and bisexual men. Use of barrier methods (condoms, dental dams) can protect against syphilis.

In related news, Kate Buchacz, PhD, from the Centers for Disease Control and Prevention (CDC) and colleagues reported in the October 21, 2004 issue of *AIDS* that syphilis is associated with higher HIV viral loads and lower CD4 cell counts. This retrospective review included data on 17 cases of primary and 35 cases of secondary syphilis in HIV positive men in San Francisco between 2001 and 2003. Among the 36 subjects with viral load results available before and during syphilis infection, HIV RNA levels increased during infection by a mean of 0.21 logs overall, and by 0.33 logs in the men with secondary syphilis. However, results varied by viral load at the time of syphilis infection; men on HAART and/or with undetectable HIV RNA were less likely to experience viral load spikes during syphilis infection than untreated men and/or those with detectable viral load. Although HIV viral load decreased after syphilis treatment, it remained above the presyphilis level. Among the 31 men with available CD4 cell measurements before and after syphilis, CD4 cell counts declined by a mean of 62 cells/mm³ during syphilis infection, with greater decreases among men with secondary syphilis and those not taking HAART.

These results indicate that syphilis likely increases HIV infectivity due to higher blood viral loads (the virus is more easily transmitted when an HIV positive person has a high viral load), as well as the presence of open sores, which allow the virus to gain entry to the body. This study underlines the importance of syphilis prevention initiatives for gay and bisexual men such as the San Francisco Department of Public Health’s “Healthy Penis” campaign.

High HIV Levels in Rectal Secretions

Levels of HIV in rectal secretions are much higher than blood or semen HIV viral loads, according to a study in the July 1, 2004 issue of *JID*. Richard Zuckerman, MD, from the University of Washington in Seattle and colleagues studied 64 HIV positive MSM in Seattle and Lima, Peru. The researchers measured significantly higher HIV levels in

rectal mucosa secretions than in semen or blood. The median HIV concentrations in the semen, blood, and rectal secretions were 3,550, 17,400, and 91,200 copies/mL, respectively. Higher HIV concentrations in rectal secretions were observed even in men taking HAART (42% of the study population), and antiretroviral therapy had less impact on rectal secretion viral load than on semen or blood viral load. Among the men on HAART, the median semen, blood, and rectal secretion viral loads were 1,000, 200, and 3,980 copies/mL, respectively; among the untreated men, the corresponding HIV RNA levels were 12,600, 63,100, and 316,000 copies/mL. In some cases, HIV was present in rectal secretions even when the virus was undetectable in the blood. However, rectal, semen, and blood viral loads were correlated; individuals who had higher HIV RNA in their blood also tended to have higher levels in their semen and rectal secretions. These results suggest that the “top” in anal sex may be at greater risk of HIV infection than previously believed, and reinforces the recommendation to use condoms for anal sex even if only the “bottom” is HIV positive.

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

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Immune Reconstitution Syndrome

Nicholas
Cheonis

Immune reconstitution, or the reversal of HIV-related immune system decline, is one of the primary goals of highly active antiretroviral therapy (HAART). Reconstitution involves an increase in functional CD4 cells to guide the immune response against pathogens such as HIV, resulting in the suppression of viral load and other beneficial outcomes.

However, immune reconstitution may trigger an inflammatory reaction in some people soon after they begin anti-HIV therapy and show signs of immunological improvement. Known as immune reconstitution syndrome (IRS) or immune reconstitution inflammatory syndrome (IRIS), this set of symptoms often resembles an AIDS-defining illness or other condition seen in people with HIV. While in most cases the symptoms of IRIS resolve after a few weeks, the syndrome may be severe or mistaken for true disease progression, and should be properly diagnosed and treated.

Syndrome Identified

Joseph A. DeSimone, MD, and colleagues from Thomas Jefferson University in Philadelphia first attempted to define IRIS in an article published in the September 19, 2000 edition of the *Annals of Internal Medicine*. These researchers had noted case reports in the medical literature in which HIV positive people appeared to develop a spectrum of illnesses after they had started and responded to HAART, with increases in CD4 cell counts and decreases in viral load. Remarkably, the individuals in these cases developed conditions associated with poor immune system function, such as *Mycobacterium avium* complex (MAC) and cryptococcal meningitis, at a time when their immune function was actually improving.

DeSimone's team also noted that such scenarios had been seen before in HIV negative people after withdrawal of immunosuppressive

medications. In these cases, the presumed reason for the apparent onset of illness was restoration of cellular (CD4 cell-guided) immunity, setting off a hypersensitivity reaction to an existing microbe or antigen in the body.

DeSimone's team concluded that the "paradoxical reactions" seen in people with HIV were also inflammatory responses to pathogens (viruses, bacteria) that were either latent (inactive, asymptomatic) or controlled by drug treatment when the immune system was seriously weakened. Once the immune system was reactivated thanks to HAART, its early, exaggerated responses were directed against these pathogens. The inflammation therefore did not signal a reactivation or worsening of a disease, but rather a protective process initiated by the body. As the immune system continued to improve with the help of HAART, the IRIS inflammation usually resolved, though often accompanied

by some form of treatment (see "Management," below).

DeSimone and his colleagues named this relatively uncommon phenomenon immune reconstitution syndrome. Their hypothesis on the nature of IRIS has since been echoed in reports by other clinicians.

Conditions Associated with Inflammatory Reactions

Immune reconstitution syndrome is associated with a variety of latent or subclinical infections, many of which are more commonly seen in people with very low CD4 cell counts. IRIS is perhaps most typically associated with mycobacterial infections (such as *M. avium*, which causes MAC) and herpesvirus infections (such as herpes zoster [shingles] and cytomegalovirus [CMV]). Skin conditions such as folliculitis (inflammation of hair follicles) or genital warts (associated with human papillomavirus, or

HPV) may be manifestations of IRIS, as may complications related to hepatitis B virus (HBV) or hepatitis C virus (HCV). (See the sidebar on this page for a more complete listing.)

In its July 2002 recommendations for antiretroviral therapy in countries with limited resources, the World Health Organization (WHO) made an important distinction between IRIS and clinical failure while on anti-HIV therapy:

“Clinical failure is defined as clinical disease progression with development of an opportunistic infection or malignancy when the drugs have been given sufficient time to induce a protective degree of immune restoration. This needs to be differentiated from an immune reconstitution syndrome which can be seen within the first several weeks after the institution of therapy if a subclinical infection is present at baseline.”

The atypical patterns of many cases of IRIS may help providers differentiate between clinical progression of an underlying disease and an immune reconstitution reaction. For example, the hallmarks of IRIS in someone previously responding to treatment for tuberculosis would be a new or worsening fever, new effusions (escape of fluid), new or worsening lymphadenopathy (enlarged lymph glands), and other uncharacteristic reactions, rather than progression of the lung disease itself. A mild case of herpes zoster or a local *M. avium* infection without bacteremia (bacteria in the blood), both seen in IRIS, would be unusual in an HIV positive individual not taking HAART. Similarly, two eye conditions—immune recovery vitritis (IRV; inflammation of the gelatinous substance filling the eyeball) and immune recovery uveitis (IRU; inflammation of the pigmented layer of the iris)—are seen exclusively in people with previous CMV retinitis infection who respond to anti-HIV therapy. (CMV retinitis is characterized by inflammation of the retina and may lead to blindness.)

diseases and pathogens associated with IRIS

- ✓ Castleman disease
- ✓ *Cryptococcus neoformans*
- ✓ cytomegalovirus (CMV)
- ✓ eosinophilic folliculitis
- ✓ Graves' disease
- ✓ Hansen's disease (leprosy)
- ✓ hepatitis B virus (HBV)
- ✓ hepatitis C virus (HCV)
- ✓ herpes simplex virus (HSV)
- ✓ herpes zoster (shingles)
- ✓ *Histoplasma capsulatum*
- ✓ human papillomavirus (HPV)
- ✓ Kaposi's sarcoma (KS)
- ✓ *Mycobacterium avium* complex (MAC)
- ✓ myopathy
- ✓ non-Hodgkin's lymphoma (NHL)
- ✓ *Pneumocystis carinii* (*P. jiroveci*) pneumonia (PCP)
- ✓ progressive multifocal leukoencephalopathy
- ✓ sarcoidosis
- ✓ systemic lupus erythematosus
- ✓ tuberculosis

Clinicians should keep in mind that a true case of progression of an underlying disease might be caused by resistance to antimicrobial drugs, nonadherence to antimicrobial therapy, an adverse drug reaction, a drug-drug interaction, or other factors. Diagnosing viral hepatitis after the initiation of HAART can be especially problematic, as hepatitis symptoms might be due to liver toxicity caused by a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) drug. Also, contrary to the WHO statement above, symptoms of IRIS may develop up to a year after beginning anti-HIV therapy.

Mechanism of Action

Immune reconstitution syndrome remains poorly understood. Its development appears to be linked not only

to increases in CD4 cell levels, but also to higher CD8 cell counts induced by HAART. An elevated CD8 cell count has been suggested as a prime contributing factor in worsening of both herpes zoster and hepatitis B or C symptoms after the initiation of anti-HIV therapy.

Researchers have also proposed that the increased activity of cytokines (chemical messengers that coordinate and regulate immune responses) contributes to some forms of IRIS. DeSimone's group pointed out that decreases in HIV viral load may alter levels of interleukin 12 (IL-12), a mediator of anticryptococcal activity, resulting in meningitis symptoms. Guillaume Foulon and colleagues from Hôpital Tenon in Paris found that interleukin 2 (IL-2) and interferon-gamma appeared to speed the development of

sarcoidosis in two subjects in the early stages of anti-HIV therapy. (Sarcoidosis is a chronic disease of unknown origin characterized by inflammatory nodules in the lymph nodes, lungs, skin, and bones.) The study authors also noted a case of sarcoidosis appearing two months after IL-2 was added to an existing antiretroviral regimen.

Incidence

The incidence (rate of new cases) of IRIS varies depending on the study, the population under investigation, and the associated pathogens involved. In one cohort of 52 subjects with previously diagnosed CMV retinitis, 19 of 30 (63%) who responded to HAART developed symptomatic IRV, compared with no cases in those who did not respond to therapy. In a different cohort of 33 similar subjects with CMV retinitis, only six (18%) developed symptomatic IRU. In a case-control study of 200 ethnically diverse subjects at King's College Hospital in London, 42 (21%) experienced an IRIS event a median of 12 weeks after starting HAART. The median CD4 cell count when HAART was started in this cohort was 172 cells/mm³, and the median HIV viral load was 36,878 copies/mL.

Though most individuals starting HAART are not likely to experience IRIS, clinicians should remain alert for any paradoxical reactions. The U.S. Food and Drug Administration (FDA) appears to be encouraging greater vigilance. In January 2004 the FDA approved package labeling revisions for indinavir (Crixivan), including a warning that "immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy (CART), including Crixivan...which may necessitate further evaluation and treatment." A similar labeling change has since been made for other antiretroviral drugs, including efavirenz (Sustiva) and Kaletra (lopinavir/ritonavir).

Risk Factors

While IRIS appears to be most prevalent in people with a severely

compromised immune system at baseline, other risk factors common to the widely varying manifestations of IRIS are difficult to identify and are often challenging to establish even within single cohorts. In the ethnically diverse cohort from London, in which 59% of subjects were black African, 10.5% were black Caribbean, 29.5% were white, and 49% were female, the most common IRIS symptoms were more severe or recurrent genital herpes and other dermatological infections. The study authors found no well-defined, independent predisposing factors.

A multivariate, retrospective analysis of 115 subjects in Houston with *Cryptococcus neoformans* infection found only two risk factors for IRIS: timing of antiretroviral therapy (initiation of HAART within 30 days of *C. neoformans* diagnosis), and a higher initial level of *C. neoformans* antigen in the cerebrospinal fluid, which suggests a greater intensity of initial infection. Interestingly, demographics, baseline CD4 cell count (which was very low among all subjects, though significantly higher in those with IRIS), type of antiretroviral therapy, and type of antifungal agents used were not associated with developing immune reconstitution syndrome. (*C. neoformans* is the fungus that causes cryptococcal meningitis, an inflammation of the membranes surrounding the brain and spinal cord, and other forms of cryptococcosis.)

Use of cytokines such as IL-2 to treat HIV infection might put some individuals at risk for developing IRIS. Furthermore, people with certain genetic mutations of their innate cytokines may be more likely to experience an inflammatory reaction after starting HAART. As Patricia Price and colleagues from Royal Perth Hospital in Australia reported in the October 18, 2002 issue of *AIDS*, cytokine mutations play a role in forms of IRIS related to mycobacterial and herpesvirus infections. For example, a certain tumor necrosis factor (TNF)-alpha mutation was found in 13

of 25 subjects (52%) with herpesvirus-related IRIS but in none of 11 subjects with mycobacterium-related IRIS.

Management

In cases in which IRIS and not disease progression can be diagnosed, different approaches to treatment have been used. Inflammatory reactions may be treated with antimicrobial agents directed at the underlying infection, including possible intensification of medications already in use. Clinicians might also treat the inflammatory component with steroids or nonsteroidal anti-inflammatory agents. Continued use of HAART may be all that is necessary for IRIS to resolve. In fact, the consensus is that antiretroviral therapy should not be stopped in almost all cases of paradoxical inflammation.

These interventions are mostly based on published case reports and other anecdotal clinical evidence, as there are currently no guidelines for managing IRIS. Nevertheless, outcomes are almost invariably better in people with IRIS than in those who are HIV positive with clinical progression of a given disease. Some outcomes, as in the French study of sarcoidosis, are similar in people with IRIS and in HIV negative individuals who develop the genuine disease.

Grounds for Optimism

While HAART-associated inflammatory reactions may be bothersome and occasionally severe, Bruce Walker, MD, of Harvard Medical School claims that the syndrome should be "grounds for great optimism." According to Walker, the IRIS phenomenon shows that functional immunity can be restored in HIV positive individuals, and that subsequent, specific immune responses can be directed toward common pathogens. The hope is that researchers will eventually find a way to bolster the body's immune responses against HIV itself using HIV-specific CD4 cells to naturally suppress the virus.

Nicholas Cheonis is editor of BETA.

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Is Your Health Going Up in Smoke?

Smoking is a habit. It is often a stress-related activity. Smoking is also a risk factor for many conditions that affect people with HIV, including cardiovascular disease, bone disease, and anal cancer.

The FDA has approved bupropion (Zyban) as a nicotine-free medicinal quitting aid. Nicotine replacement therapies—in the form of lozenges (Commit), patches (Habitrol, NicoDerm CQ, Nicotrol), inhalers (Nicotrol Inhaler), and gum (Nicorette)—are another means of quitting. Complementary methods include behavior modification, counseling and support, and acupuncture.

The Stop Smoking Center (www.stopsmokingcenter.net) is a unique web site that offers a Quit Program, online support services, and links to a wide range of smoking cessation resources, including the American Lung Association (212-315-8700) and Nicotine Anonymous (415-750-0328).

The Tobacco Education Center of UCSF/Mt. Zion (415-885-7895) is a quitting resource for San Francisco Bay Area residents.

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AAHIVM DOCS

Among several first-line antiretroviral regimens for treatment-naïve people recommended by the U.S. Department of Health and Human Services (DHHS)*, the following two are designated as “preferred”:

NNRTI-based

efavirenz (Sustiva)
+ 3TC (lamivudine, Epivir) *or* FTC (emtricitabine, Emtriva)
+ AZT (zidovudine, Retrovir) *or* tenofovir DF (Viread)

PI-based

Kaletra (lopinavir/ritonavir)
+ 3TC *or* FTC
+ AZT

Other first-line regimens are considered “alternative,” although the guidelines state that “based on individual patient characteristics, a regimen listed as alternative...may actually be the preferred regimen for a selected patient.”

With these recommendations in mind, *BETA* asked board members of the American Academy of HIV Medicine (AAHIVM)** the following question:

What first-line regimen do you recommend for different populations, and why?

Jonathan Appelbaum, MD

Fenway Community Health, Boston

Generally, I use efavirenz with Truvada [FTC/tenofovir] as my first-line therapy for most patients. For women who are pregnant or planning to become pregnant, I still use nelfinavir [Viracept] and Combivir [AZT/3TC]. For populations with low CD4 cell counts (below 100 cells/mm³) and/or viral loads over 100,000 copies/mL, I tend to start with a boosted protease inhibitor such as Kaletra or boosted atazanavir [Reyataz] with Combivir or Truvada. For African Americans I try to use efavirenz, but if there are problems with tolerance I will switch to either nevirapine [Viramune] or to boosted atazanavir.

Judith Feinberg, MD

University of Cincinnati College of Medicine

The way I conceptualize and deal with first regimens is absolutely individualized to a given patient and his or her situation.

Marah J. Lee, DO, FACP

Private practice, Ft. Lauderdale

I recommend either Combivir with fosamprenavir [Lexiva] twice daily, or Epzicom [3TC/abacavir] with Lexiva, depending on the patient’s daily habits. With these combinations, I see a rapid decline in viral load and good tolerability.

Michelle Roland, MD

University of California, San Francisco

I don’t have a single first-line regimen for any population. I make recommendations based upon a series of questions about the patient’s life patterns (such as sleeping and eating) and preferences (pill number, size, type, and texture; concerns about PI side effects; concerns about NNRTI resistance) and their assessment of their adherence likelihood.

John Stansell, MD

Positive Health Program, San Francisco General Hospital

This is a complex question. All therapy needs to be based on viral susceptibility and the patient’s drug tolerance, but for the naïve patient with adequate immune reserve (i.e., over 100 CD4 cells/mm³), I would generally start with a once-daily regimen. First-line is probably tenofovir/3TC/efavirenz. If the patient is reluctant to take efavirenz, I will use tenofovir/3TC/boosted atazanavir. If they don’t want to use a PI, I try twice-daily nevirapine. For the person presenting with advanced disease, say after an OI, I use a Kaletra-based regimen.

These are gross generalities. The nuance of antiretroviral use is the art of HIV management.

**The nuance of antiretroviral use
is the art of HIV management.**

**IN
THEIR
OWN
WORDS**

Aimee Wilkin, MD, MPH

Wake Forest University School of Medicine, Winston-Salem

In general, I tailor first-line regimens based on a discussion with the patient regarding lifestyle, feelings about a once-a-day regimen, predictable side effects, and other medical problems such as kidney disease, liver disease, and depression. A typical choice would be two NRTIs in a combination pill plus an NNRTI (usually Truvada/efavirenz or Combivir/efavirenz). For patients who might not do well with an NNRTI, I'd use a boosted PI regimen with two NRTIs. There are at least three choices for a good boosted PI regimen, and the choice varies depending on the predicted side effect profile, drug interactions, and other medical problems that the patient has.

* Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents from the DHHS was last updated October 29, 2004. The complete document is available online at www.aidsinfo.nih.gov/guidelines.

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MORTALITY TRENDS:

Toward a New Definition of AIDS?

Liz
Highleyman

HIV disease today looks very different than it did two decades ago when the first cases were described—at least in developed countries where highly active antiretroviral therapy (HAART) is widely available. Most HIV positive people receiving treatment no longer succumb to opportunistic illnesses (OIs) that take advantage of their ravaged immune systems. Instead, people with HIV now live longer and die from a wide variety of other causes. In other words, a growing number of positive people will die with HIV, but not of HIV.

In the HAART era, HIV positive people and their health-care providers must now think about the cumulative impact of chronic HIV infection and the long-term side effects of treatment. In addition, as effective antiretroviral therapy extends the lives of people with HIV, they become prone to conditions that normally occur with greater frequency as people age (such as heart disease, diabetes, and osteoporosis) and progressive conditions that may take decades to cause significant illness or death (such as chronic viral hepatitis). Given the shifts in the types of conditions now seen in people with HIV, it may be time to rethink the definition of AIDS.

Changing Patterns of Mortality

In the 1980s and early 1990s, HIV/AIDS was a major cause of death among adults in the U.S., with the mortality (death) rate climbing every year from 1987 to 1994. By the latter year, the disease had become the leading cause of death among adults 25–44 years of age. A significant decrease in AIDS mortality first became apparent in 1996, the year after the first protease inhibitor (PI) was introduced. In 1997 the number of HIV/AIDS deaths fell by nearly 50%, followed by a further 20% reduction in 1998. By 1999, however, the decline had leveled off. According to the Centers for Disease Control and Prevention (CDC), HIV/AIDS deaths fell from more than 51,000 in 1995 to

about 16,000 in 2002 (the latest year for which data are available).

In 2002 HIV/AIDS was the fifth leading cause of death for adults aged 25–44, but not in the top 15 for the population as a whole. It is important to emphasize, however, that the overall HIV/AIDS mortality rate hides differences among demographic groups. In 1996, for example, while HIV/AIDS deaths dropped by 20% among white people, the rate declined by just 2% among black individuals. The decrease among men who have sex with men was three times as great as that for injection drug users (IDUs), while the mortality rate actually rose for people infected through heterosexual contact. And in 2001 HIV/AIDS remained the leading cause of death for black women aged 25–34, compared with the third leading cause for

black men, sixth for white men, and seventh for white women in the same age group.

Looking at the population as a whole, the top three causes of death in 2002 were heart disease, cancer, and stroke, followed by diabetes at number six and chronic liver disease/cirrhosis at number 12. As discussed below, these conditions now account for a growing proportion of deaths among people with HIV as well.

AIDS Then and Now

Perhaps the most evident change in the epidemic over the past 20 years has been the increase in the length of time people with access to good health care can expect to live after testing HIV positive or being diagnosed with AIDS. According to Dennis Osmond, PhD, of the University of

California at San Francisco, in the earliest years of the epidemic individuals could expect to live about one year after an AIDS diagnosis. Survival times with AIDS began to increase in the mid-1980s as OI treatment improved. With the wider use of OI prophylaxis (preventive therapy), the time between seroconversion and an AIDS diagnosis increased as well. The introduction of PIs in 1995—which enabled the construction of potent combination regimens consisting of drugs from two or more classes—led to a tremendous expansion of time between seroconversion and progression to AIDS or death. In the Multicenter AIDS Cohort Study (MACS), for example, the estimated time from seroconversion to death for a person infected at age 30 rose to a median of about 13 years by the 1995–1997 period.

Today many individuals have survived—and even thrived—with HIV for upwards of two decades. Because HIV/AIDS is still a relatively young disease, it is too soon to know the upper limit of survival for HIV positive people on HAART. While the long-term toxicities of antiretroviral therapy remain an urgent concern, some experts now cautiously predict that HIV positive people who receive optimal care may ultimately live a near-normal lifespan.

Who Gets AIDS Today?

Where HAART is widely available, many people starting treatment in recent years have never reached a CD4 cell nadir (lowest-ever level) below 200 cells/mm³ or developed an AIDS-defining OI. Those who do typically fall into one of the following categories:

- individuals who have been infected with HIV for a long time and may have previously received suboptimal treatment—including nucleoside reverse transcriptase inhibitor (NRTI) monotherapy—before the advent of HAART; such people often have HIV that is resistant to

many drugs and thus have limited treatment options

- people who have access to effective HAART, but either are not able to tolerate the drugs or fail to achieve adequate adherence
- individuals who cannot afford anti-retroviral therapy and are unable to

access benefits through programs such as Medicaid or state AIDS Drug Assistance Programs (ADAPs)

- people who have never been tested for HIV and do not seek care until they have already experienced significant immune system decline and perhaps developed AIDS-related symptoms.

how is AIDS defined?

The CDC's first AIDS surveillance case definition, which went into effect in 1983, included opportunistic illnesses (OIs) most commonly seen in the first groups affected by the disease, primarily gay men. As more was learned about the syndrome, the definition was revised in 1985 and again in 1987. In 1993 the agency added new conditions to better reflect the nature of AIDS in other populations. But the biggest change that year was the addition of a CD4 cell count cutoff of 200 cells/mm³ (or CD4 cell percentage of 14%). Under this new criterion, individuals with compromised immune function could be diagnosed as having AIDS even if they were asymptomatic and had not yet developed OIs.

1987 AIDS surveillance definition for adults:

Candidiasis of the esophagus, bronchi, trachea, or lungs
 Coccidioidomycosis, disseminated or extrapulmonary
 Cryptococcosis, extrapulmonary
 Cryptosporidiosis, chronic intestinal
 Cytomegalovirus (CMV) disease
 Cytomegalovirus retinitis
 Encephalopathy, HIV-related (AIDS dementia complex)
 Herpes simplex virus (HSV), chronic ulcer(s)
 Herpes simplex bronchitis, pneumonitis, or esophagitis
 Histoplasmosis, disseminated or extrapulmonary
 Isosporiasis, chronic intestinal
 Kaposi's sarcoma (KS)
 Lymphoma: non-Hodgkin's (NHL), primary brain/CNS
Mycobacterium avium/kansasii complex (MAC)
Mycobacterium tuberculosis (TB), extrapulmonary
Mycobacterium, other species, disseminated or extrapulmonary
Pneumocystis carinii pneumonia (PCP) (now called *P. jiroveci*)
 Progressive multifocal leukoencephalopathy (PML)
Salmonella septicemia, recurrent
 Toxoplasmosis of the brain
 Wasting syndrome

Added in the 1993 revision:

Invasive cervical cancer
 Pneumonia (other than PCP), recurrent
 Pulmonary tuberculosis
 CD4 cell count below 200 cells/mm³

The CDC estimates that as many as two-thirds of people living with HIV in the U.S. do not know they are infected, and nearly one-half are diagnosed after their immune function has already markedly declined. Such cases are most often seen among marginalized populations (including racial/ethnic minorities, the homeless, and IDUs) and tend to be concentrated in inner cities. Socioeconomic factors such as poverty, substance use, and coexisting psychiatric illnesses can have a profound impact on access to and success of anti-HIV therapy.

Several studies presented at the XV International AIDS Conference held this past summer in Bangkok looked at factors associated with late testing and treatment. Scott Kellerman, MD, and J. Blair from the CDC found that 1,175 of 2,063 people (57%) seen in Boston, Chicago, Hartford, Los Angeles, and San Francisco received an AIDS diagnosis within just six months of first testing HIV positive. The chances of late HIV detection were greater among African Americans (1.4 times as high as whites), Latinos/Hispanics (1.7 times as high), and individuals over age 40. African Americans were twice as likely as whites to develop AIDS before receiving antiretroviral therapy. A study from North Carolina found that late presentation was linked to male sex and living in a rural area. And an analysis of the French Hospital Database on HIV presented by Murielle Mary-Krause, MD, and colleagues showed late treatment to be associated with older age, HIV acquisition by a route other than male-to-male sex, and immigration from sub-Saharan Africa.

It is hoped that the CDC's recently announced emphasis on routine testing, along with the availability of a new rapid oral HIV test, will reduce the number of people who are unaware that they harbor HIV. Offering regular testing to individuals at risk can help bring more people into treatment earlier in the

course of their disease, when antiretroviral therapy can do the most good.

How Late Is Too Late?

Treatment of late-diagnosed individuals can be challenging, since they may require treatment or prophylaxis for OIs in addition to HAART, thereby increasing the risk of additive side effects and drug interactions. In addition, people who start HAART with low CD4 cell counts and/or high HIV viral loads remain at greater risk for progression to an AIDS-defining illness or death compared with those who start therapy with less compromised immune function.

For example, Andrew Phillips and colleagues with the CASCADE Collaboration reported in the January 2, 2004 issue of *AIDS* that the short-term risk of progression to AIDS rose in a linear fashion as CD4 cell count decreased and as HIV viral load and age increased. While a 25-year-old individual with 500 CD4 cells/mm³ and a viral load of 3,000 copies/mL had a miniscule 0.3% probability of developing AIDS within six months (chosen as a typical interval between clinic visits), the rate climbed to 44.8% for a 55-year-old person with 50 CD4 cells/mm³ and a viral load of 300,000 copies/mL. (For a detailed chart entitled "Predicted 6-month risk of AIDS according to age and current CD4 cell count and viral load," see the October 2004 adult U.S. federal treatment guidelines, table 3b, at <http://aidsinfo.nih.gov>.)

Data from the ART Cohort Collaboration illustrate the perils of late treatment. Matthias Egger, MD, and colleagues reported findings based on an analysis of some 12,500 participants in a dozen American and European clinical trials in the July 13, 2002 issue of *The Lancet*, and presented an update at the Bangkok AIDS conference. In this analysis, progression to AIDS or death was strongly associated with viral loads above 100,000 copies/mL and lower baseline CD4 cell counts, with risk

increasing as counts fell below 350, 200, 100, and 50 CD4 cells/mm³. The rate of progression among individuals starting anti-HIV treatment with fewer than 50 cells/mm³ was five times as high as the rate among people with more than 350 cells/mm³. Starting therapy with CD4 cell counts above 350 cells/mm³ did not appreciably improve outcomes, however, lending support to the 350 cells/mm³ threshold recommended in the U.S. HIV treatment guidelines. But another analysis of the ART Cohort presented at the same conference by Caroline Sabin showed an increased risk of progression among individuals starting treatment with 200–350 CD4 cells/mm³, and other research suggests that IDUs may need to initiate antiretroviral therapy at higher CD4 counts to derive the same benefit that non-IDUs get from starting at lower CD4 cell levels (see "News Briefs" on page 9), so the question as to whether people within this range should start therapy remains somewhat murky.

Despite abundant evidence that deteriorating immune function and increasing HIV viral load levels are associated with a greater risk of progression to AIDS or death, research on the whole indicates that even people who begin treatment with severe immunosuppression, very low CD4 cell counts, high viral loads, and/or symptomatic AIDS can still derive significant benefit from antiretroviral therapy. For example, S. Koltar and colleagues reported in the November 15, 2004 issue of *Clinical Infectious Diseases (CID)* that in the ACTG 362 study, which included 612 participants followed for 3–5 years, HIV disease progression was uncommon (1.75 new AIDS-defining conditions per 100 person-years [PY]) in people who started HAART with CD4 cell counts below 50 cells/mm³—62% of whom had previously been diagnosed with at least one AIDS-defining illness—as long as they were then able to achieve sustained CD4 cell

increases of at least 100 cells/mm³ and maintain low HIV viral loads.

AIDS vs Non-AIDS Mortality

Dying with HIV disease today is not the same as dying of AIDS a decade or two ago. As the number of deaths due to OIs and other AIDS-defining conditions has fallen, the proportion of deaths due to all other causes has consequently risen. Importantly, such a shift does not necessarily indicate an absolute increase in the number of non-AIDS deaths, since a rising proportion of deaths due to one cause may simply reflect a falling proportion of deaths due to another.

One of the best snapshots of the epidemic is the HIV Outpatient Study (HOPS), which monitors more than 5,500 participants at a dozen U.S. HIV clinics. A HOPS analysis published in the March 26, 1998 issue of the *New England Journal of Medicine (NEJM)* was the first to show a marked decline in mortality at the dawn of the HAART era. Among the 1,255 subjects then in the database, the overall death rate decreased from 29.4 per 100 PY in 1995 to 8.8 per 100 PY in mid-1997. According to an update presented by Frank Palella, MD, at the 11th Conference on Retroviruses and Opportunistic Infections in February 2004, the mortality rate was 2.2 per 100 PY in 2002—a figure that has been roughly stable since 1998. Between 1996 and 2002 the proportion of non-OI deaths rose from 46% to 72%. “If someone takes [HAART], they will live longer and when death occurs, it will not be due to an AIDS-related condition,” Dr. Palella concluded.

Looking at a large European cohort, Amanda Mocroft, PhD, and colleagues reported in the August 16, 2002 issue of *AIDS* that in the EuroSIDA cohort, which includes more than 8,500 HIV positive participants, the overall death rate fell from 15.6 to 2.7 per 100 PY between 1994

and 2001. In addition, the proportion of AIDS deaths decreased by 23%, while the proportion of non-AIDS deaths rose by 32% during the same period. Similarly, Ard van Sighem and colleagues with the Dutch ATHENA study reported in the October 17, 2003 issue of the same journal that among more than 3,700 participants using HAART, HIV-related mortality decreased from 3.8 to 0.7 per 100 PY between 1996 and 2000, while non-HIV-related mortality remained constant. (This research team defined deaths related to antiretroviral therapy as non-HIV-related.)

Finally, in the October 18, 2003 issue of *The Lancet*, Kholoud Porter, MD, and colleagues, also with the CASCADE Collaboration, reported on a study of 7,740 participants from 22 cohorts in Europe, Australia, and Canada, categorized into three groups based on when they seroconverted: pre-1997 (when HAART was introduced in these countries), 1997–1998 (limited HAART), or 1999–2001 (widespread HAART). By 1997 the rate of AIDS-related deaths had decreased by about 50%, and by 2001 it had fallen by 80%.

Shifting Causes of Illness and Death

A wide variety of conditions fall within the broad category of “non-OI” or “non-AIDS-related” causes of morbidity (illness) and mortality. These include age-related conditions such as cardiovascular disease and diabetes, as well as toxicities associated with antiretroviral therapy.

In Dr. Koltar’s ACTG 362 cohort, five participants died of AIDS-related causes between 1997 and 2002, while five died of cardiovascular conditions and five due to liver failure related to hepatitis B or C virus (HBV and HCV, respectively). In Dr. Palella’s HOPS cohort, deaths due to three major OIs—*Pneumocystis carinii* (now *P. jirovecii*) pneumonia (PCP), *Mycobacterium avium* complex (MAC), and cytomegalovirus

(CMV)—declined from 21.9 per 100 PY to 3.7 per 100 PY between 1994 and mid-1997. In the 2000–2002 period the most common non-OI causes of death were liver (36%), lung (23%), cardiovascular (17%), and kidney (10%) conditions.

In a different type of analysis, Richard Selik, MD, of the CDC and colleagues examined death certificate data for all deaths in the U.S. between 1987 and 1999; results were published in the April 1, 2002 issue of the *Journal of Acquired Immune Deficiency Syndromes (JAIDS)*. From 1995 to 1999, rates of several AIDS-defining illnesses declined, including Kaposi’s sarcoma (5% to 3%), CMV (7% to 3%), HIV encephalopathy (6% to 4%), and wasting (10% to 7%). At the same time, rates of deaths due to certain non-AIDS causes rose: septicemia (blood poisoning; 9% to 13%), liver disease (5% to 12%), kidney disease (6% to 9%), and heart disease (4% to 7%). The researchers suggested that improved OI prophylaxis and treatment likely contributed to decreased OI rates, while toxicity associated with antiretroviral therapy may have contributed to higher rates of liver, kidney, and heart problems. At the 2004 Retrovirus conference Dr. Selik presented 1987–1999 death certificate data for San Francisco and New York City—two early epicenters of the epidemic—showing that non-AIDS deaths rose from 11% to 23% during the study period.

While most studies have shown a decline in AIDS-related mortality, proportions and absolute numbers of deaths vary considerably by locale and demographic group. At the 2001 Retrovirus conference, S. Ahmad from Chicago’s Cook County Hospital presented data from a retrospective chart review of all HIV inpatient deaths between January 1998 and September 2000. This patient population was predominantly comprised of substance-using African American men. Among those who died, more than half were not receiving antiretroviral therapy

and about half had CD4 cell counts below 50 cells/mm³. It is therefore not surprising that OIs remained common in this cohort, accounting for about 60% of all deaths. These results underline the importance of improving access to care and promoting early testing and treatment, especially among marginalized populations.

As the relative proportion of OI- or AIDS-related deaths among HIV positive people has decreased, certain non-AIDS-defining conditions have received particular attention as important new threats for people living with HIV. Liver problems are sometimes related to antiretroviral drug toxicity, but liver damage due to chronic viral hepatitis is a growing concern as people coinfecting with HIV plus HBV and/or HCV live longer thanks to HAART. But HAART itself can lead to new problems, as exemplified by the potential for increased risk of cardiovascular disease due to blood lipid (fat) and glucose (sugar) elevations associated with PI-based therapy. Trends in AIDS-defining and non-AIDS-related malignancies (cancers) are less clear, but most research indicates that HIV positive individuals face a higher cancer risk than their HIV negative counterparts. Liver problems, heart disease, and malignancies in people with HIV will be discussed in detail in the following sections.

Liver Problems

Liver problems in people with HIV tend to fall into two categories: progressive liver damage due to chronic viral hepatitis coinfection, and hepatotoxicity (liver toxicity) associated with certain antiretroviral drugs.

In the HAART era liver disease has become a major cause of hospitalization and death among people with HIV. In the February 1, 2001 issue of *CID*, for example, Iona Bica, MD, and colleagues reported that during the 1998–1999 period, 50% of deaths (11 of 22) of HIV positive people at Boston's New England Medical Center were due to end-stage liver disease (ESLD), compared with 12% in 1991.

In Dr. Ahmad's study of patients at Cook County Hospital (about half of whom were coinfecting with HCV), ESLD was the second leading cause of mortality, accounting for 35% of deaths. And in the Women's Interagency HIV Study (WIHS), liver disease was the leading non-AIDS cause of mortality in the 1994–2000 period, accounting for about 20% of all deaths.

A similar situation exists in Europe, especially in Spain and Italy. At the Instituto de Salud Carlos III in Madrid, ESLD was responsible for 43% of deaths of people with HIV in 2000, about one-third of whom were coinfecting with HCV. In the French Aquitaine cohort, HCV-related ESLD was the number one cause of mortality in the 1998–1999 period (accounting for 29% of deaths), while in the EuroSIDA cohort liver-related mortality has been a leading cause of death since 2000.

Chronic Viral Hepatitis

About one-quarter of people with chronic hepatitis B or C will experience progression to liver fibrosis (buildup of fibrous tissue), cirrhosis (scarring), and/or hepatocellular carcinoma (a type of liver cancer), a process that typically takes 10–40 years. Before the advent of HAART, coinfecting individuals and those with HIV alone fared similarly, because most died of AIDS-related causes before ESLD developed. Today this picture has changed. As reported in the October 21, 2004 issue of *AIDS*, Maurizio Bonacini, MD, and colleagues reported that HIV positive individuals coinfecting with both HBV and HCV were twice as likely to die of a liver-related cause as those with either HIV/HBV or HIV/HCV, who in turn had about twice the risk as people with HIV alone (28%, 13–15%, and 6%, respectively).

Some HIV positive people coinfecting with HCV and/or chronic active HBV are more likely to progress to serious liver disease, and to progress more rapidly, than those

with viral hepatitis alone. (For more on this topic, see "HIV and Hepatitis Coinfection," *BETA*, Winter 2003.) At a June 2002 National Institutes of Health (NIH) consensus conference on management of hepatitis C, David Thomas, MD, cited a meta-analysis showing that HIV/HCV-coinfecting people had a two-fold greater risk of cirrhosis and a six-fold greater risk of ESLD than those with HCV alone. Abdul Mohsen and colleagues from King's College in London estimated that the average time from HCV infection to the onset of cirrhosis was 23 years in coinfecting people, compared with 32 years in people with HCV alone.

However, much early research on coinfection was conducted before the advent of HAART. More recent studies suggest that accelerated liver disease progression may be a consequence of compromised immune function, and that HIV positive people with well-controlled HIV disease may do as well as their HIV negative counterparts. Based on a case-control study of 116 HIV/HCV-coinfecting subjects and 235 individuals with hepatitis C alone, for example, Eugenia Mariné-Barjoan and colleagues reported in the November 5, 2004 issue of *AIDS* that liver fibrosis progressed significantly more slowly in people who had been on HAART longer and in those who had a shorter interval between presumed HCV infection and initiation of anti-HIV therapy.

Research is less clear about the impact of hepatitis C on HIV disease. A majority of studies indicate that it does not have a detrimental effect. For example, Ellen Tedaldi, MD, and colleagues reported in the February 1, 2004 *CID* that among a cohort of 823 HIV positive individuals, those who were coinfecting with HCV did not have a higher rate of progression to AIDS than those with HIV alone.

Other research supports the opposite conclusion. In the Swiss HIV Cohort of more than 3,000 participants, HIV/HCV-coinfecting individuals were more likely to develop OIs

(8% vs 5%) and more than twice as likely to die of any cause (9% vs 4%) than those with HIV alone.

Studies more consistently show that HIV/HCV-coinfected individuals experience slower immune recovery after starting antiretroviral therapy. For example, J. Martin, MD, and colleagues determined that after two years on HAART, CD4 cell counts increased by an average of 53 cells/mm³ in coinfecting people compared with 111 cells/mm³ in those with HIV alone.

Fortunately, treatment for hepatitis C has improved in recent years with the adoption of pegylated interferon (Pegasys or Peg-Intron) plus ribavirin. While coinfecting individuals do not respond as well to interferon-based therapy as those with HCV alone, recent research has yielded increasingly promising results. In the APRICOT study, which included 868 coinfecting individuals in 19 countries, those treated with Pegasys/ribavirin for 48 weeks had a sustained virological response (SVR) rate of 40% (62% for subjects with HCV genotypes 2 or 3; 29% for those with genotype 1, which is most common in the U.S. and is more difficult to treat). SVR refers to continued undetectable HCV viral load six months after the end of treatment. In study ACTG 5071, which included 133 coinfecting subjects, the SVR rate using the same regimen was 27% (73% for genotypes 2 or 3; 14% for genotype 1). Both studies were reported in the July 29, 2004 issue of *NEJM*.

The French RIBAVIC study (presented at the 2004 Retrovirus conference), which included 142 participants, produced a less impressive SVR rate of 26% (43% for genotypes 2 or 3; 11% for genotype 1) using Peg-Intron/ribavirin. In the September 3, 2004 issue of *AIDS*, Montserrat Laguno and colleagues from Barcelona reported an SVR rate of 44% for Peg-Intron/ribavirin (53% for genotypes 2 or 3; 38% for genotype 1) in a study of 95 coinfecting participants—the highest seen to date in coinfecting individuals with genotype 1.

It is unclear why the SVR rates varied so much among these four studies. ACTG 5071 included more black individuals (about 33%) than APRICOT (about 10%); blacks as a group respond less well to interferon. RIBAVIC included subjects with more advanced liver damage, and rates of dropouts and severe adverse events were considerably higher.

Most people with HIV/HCV-coinfection can be successfully treated for both diseases. While not everyone with HCV needs treatment, which is indicated only if liver disease is progressing, some experts believe that coinfecting individuals should receive treatment for HCV early, in light of the more rapid liver disease progression in this group.

Because people with higher CD4 cell counts respond better and are better able to tolerate the side effects of interferon, experts often recommend initiating HAART to improve immunological function before starting HCV treatment. An international consensus panel has recommended that coinfecting individuals considering HCV treatment should have a CD4 cell count of at least 350 cells/mm³; HCV therapy is not recommended for people with fewer than 200 cells/mm³. On the other hand, if a person has early-stage HIV disease (with a high CD4 count and low HIV viral load) but advancing liver damage, it may be more appropriate to complete HCV treatment—which may improve the liver's ability to tolerate antiretroviral drugs—before starting HAART.

Hepatitis B also progresses more rapidly in people with HIV. As with hepatitis C, many people with chronic hepatitis B do not need treatment. Three drugs are currently approved to treat HBV: conventional interferon, 3TC (lamivudine, Epivir), and adefovir (Hepsera). 3TC and two experimental anti-HBV drugs—FTC (emtricitabine, Emtriva) and tenofovir DF (Viread)—work against HIV as well as HBV (the latter two are approved for this indication; adefovir at higher doses was a failed

experimental anti-HIV agent). HIV/HBV-coinfected individuals should consider including one of these dually active agents as part of their HAART regimens, but should be aware that discontinuing these drugs can lead to worsened hepatitis symptoms (“flares”).

Drug-Related Liver Toxicity

The second important liver-related problem for HIV positive people is toxicity associated with certain anti-HIV drugs, often indicated by elevated liver enzyme (ALT and AST) levels. Among the protease inhibitor drugs, full-dose ritonavir (Norvir) is the worst offender, though the lower ritonavir doses used to boost other PIs are less likely to cause hepatotoxicity. Nevirapine (Viramune) can cause a hypersensitivity reaction characterized by liver inflammation and skin rash; this is

healthy liver tips

- Get vaccinated against hepatitis A and hepatitis B
- Abstain from drinking alcohol; studies clearly show that alcohol worsens liver damage
- Be cautious about using street drugs, prescription drugs, over-the-counter medications (especially acetaminophen, e.g., Tylenol), and herbal remedies
- Report all use of drugs and herbs to health-care providers
- Avoid exposure to environmental toxins such as solvents, paint thinners, and pesticides
- Get regular, moderate exercise
- Get regular health check-ups, including liver enzyme monitoring

most likely to occur in women with more than 250 CD4 cells/mm³ and men with more than 400 CD4 cells/mm³.

Several studies have shown that people with existing liver disease, including chronic viral hepatitis, are more prone to drug-related liver toxicity. Ronald Reisler, MD, MPH, and colleagues reported in the December 1, 2003 issue of *JAIDS* that in a cohort of 2,947 individuals receiving anti-retroviral therapy, HCV coinfection significantly increased the risk of grade 4 (life-threatening) liver-related adverse effects relative to the rate in people with HIV alone. But overall, the rate of serious liver toxicity is very low, even among coinfecting individuals. Nevertheless, HIV positive people taking HAART—whether or not they have viral hepatitis—should receive regular tests to monitor liver function.

Cardiovascular Disease

Among the population as a whole, heart disease is the leading cause of death, and cerebrovascular disease is third. (Cerebrovascular refers to blood vessels of the brain; see “Neurological Complications of HIV/AIDS” on page 37.) Thus it is no surprise that as HAART keeps HIV positive people alive longer, they too are increasingly likely to succumb to cardiovascular problems.

Yet there is growing concern that cardiovascular disease in people with HIV is not just an expected hazard of aging, but is also linked to antiretroviral therapy itself. Long-term studies show that PIs as a class are associated with metabolic side effects that were not seen in initial clinical trials, including unfavorable blood lipid profiles (elevated triglycerides and LDL “bad” cholesterol, and low HDL “good” cholesterol), insulin resistance, and diabetes mellitus—all of which are known risk factors for atherosclerotic heart disease (hardening of the arteries) in the general population. (For more on this topic, see “Cardiovascular Disease in People

with HIV,” *BETA*, Summer/Autumn 2002; and “Insulin Resistance and Diabetes,” *BETA*, Winter 2004.)

Although there is every reason to expect that these risk factors will also hold for HIV positive people, it is not yet clear whether rates of heart disease and cardiovascular events such as myocardial infarction (heart attack) and stroke have increased since the advent of HAART. In Dr. Selik’s death certificate analysis, heart disease had become the fifth leading cause of death among HIV positive people by 1999. In the EuroSIDA study, myocardial infarction was the second leading cause of mortality after liver disease. In the HOPS cohort during the 1993–2001 study period, individuals using a PI were more likely to have heart attacks (13 of 3,013 participants, or about 4%) than those not using this class of drugs (2 of 2,663 participants, or about 0.8%). In contrast, a retrospective analysis of the medical records of more than 36,700 HIV positive veterans by Samuel Bozzette, MD, found a small (10–20%) decrease in the rate of hospital admissions and deaths due to heart attacks and strokes since HAART became widely available.

Because events such as heart attacks and strokes occur relatively infrequently, large observational studies provide some of the most valuable data about rates of cardiovascular problems over time. One such study called D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) includes more than 23,000 HIV positive individuals at 188 clinics in the U.S., Europe, and Australia, about three-quarters of whom are on HAART.

In the November 20, 2003 issue of *NEJM*, the D:A:D researchers reported that between December 1999 and February 2002, 126 subjects experienced myocardial infarctions, and the risk increased with duration of antiretroviral therapy—a 26% relative increase per year of HAART exposure. Nevertheless, at the 2004 Retrovirus conference the same group reported that the myocardial infarction rate

among HIV positive individuals on HAART was “of a similar magnitude to, or somewhat higher than” the rate seen in the Framingham Heart Study, a long-term study of cardiovascular risk in the general population. Importantly, the absolute rate of heart attacks among D:A:D study participants was low: about one per 250 individuals taking HAART for four years (or 3.5 per 1,000 PY). More recently, in the September 3, 2004 issue of *AIDS*, the D:A:D team reported that HAART use was also associated with an increased risk of stroke and a greater likelihood that a participant would require invasive heart procedures.

In studies such as HOPS and D:A:D, traditional cardiovascular risk factors—such as male sex, older age, smoking, and family history of heart disease—are as or more important than HAART and its associated metabolic side effects. As such, HIV positive individuals should take the same measures to promote heart health as recommended for the general population, including maintaining a healthy weight, getting regular exercise, and quitting smoking.



HAART drug substitution may also play a role. Numerous studies have shown that switching from a PI-based regimen to one built around a non-nucleoside reverse transcriptase inhibitor (NNRTI) can improve blood lipid profiles and insulin resistance, and may even increase levels of HDL “good” cholesterol. Individuals who need the potency of a PI may consider switching to one of the newer drugs in this class—atazanavir (Reyataz) or fosamprenavir (Lexiva)—that are less associated with unfavorable blood lipid and glucose profiles.

If lifestyle changes do not adequately control blood lipid and glucose abnormalities, and if HAART regimen alteration is not feasible, physicians can prescribe adjunct therapies, such as statins and glitazones, for their HIV positive patients. It is important, however, to be aware of the potential for interactions between these medications and antiretroviral drugs.

Malignancies

The shift in mortality among people with HIV is particularly evident when looking at malignancies. Over the past two decades, rates of AIDS-defining cancers—Kaposi’s sarcoma (KS), non-Hodgkin’s lymphoma (NHL), and invasive cervical cancer—have declined overall. Looking at about 5,400 HIV positive participants drawn from the HOPS cohort and 6,700 more from two Chicago HIV clinics, for example, Pragna Patel, PhD, from the CDC reported at the 2004 Retrovirus conference that rates of KS and invasive cervical cancer, but not NHL, decreased between 1992 and 2000. Fabrice Bonnet, MD, and colleagues found that, as a percentage of total mortality, cancer accounted for 269 of 964 deaths (28%) among HIV positive people at French hospitals in 2000, with similar proportions due to AIDS-defining and non-AIDS-defining malignancies.

In the November 1, 2004 issue of *CID*, Roger Bedimo, MD, and colleagues reported a decline in AIDS-

related cancers, accompanied by a significant increase in non-AIDS-defining malignancies, in a cohort of more than 2,800 subjects at the University of Alabama at Birmingham HIV Outpatient Clinic. Altogether, the researchers tallied 178 new cases of AIDS-defining cancer and 60 new cases of non-AIDS-defining cancer (Hodgkin’s lymphoma, skin cancer, invasive anal cancer, colon cancer, lung cancer, breast cancer, kidney cancer, and head and neck cancer). Comparing pre-HAART (1989–1996) and post-HAART (1997–2002) periods, they determined that the rate of AIDS-defining malignancies fell from 40 to 11.33 cases per 1,000 PY between the two periods, while the incidence of non-AIDS-defining cancers increased from 3.27 to 10.87 cases per 1,000 PY. In this study, both nadir CD4 cell counts (22 vs 78 cells/mm³) and CD4 cell counts at the time of cancer diagnosis (38 vs 277 cells/mm³) were lower among subjects with AIDS-defining cancers than among those with non-AIDS-defining malignancies.

It is not surprising that AIDS-defining cancers are linked to immune suppression, since these malignancies are associated with viruses that appear to act in an opportunistic manner: Kaposi’s sarcoma-associated herpesvirus (KSHV, also known as human herpesvirus 8) for KS, human papillomavirus (HPV) for cervical cancer, and possibly Epstein-Barr virus (EBV) for NHL. In Dr. Patel’s study, people with lower nadir CD4 cell counts were also at increased risk for non-AIDS-defining malignancies, suggesting that even cancers not known to be associated with oncogenic (cancer-causing) viruses are more likely to occur when the immune system is suppressed, perhaps because immune surveillance and destruction of emerging cancers is diminished.

While immune reconstitution subsequent to anti-HIV therapy appears to lower the rate of certain malignancies, most research indicates

that HIV positive people remain at higher overall risk for cancer than their HIV negative counterparts. As reported in the August 1, 2004 issue of *AIDS*, for example, women in the WIHS cohort had higher incidence rates of all types of cancer compared with the general population (as determined from cancer registry data).

As antiretroviral therapy keeps HIV positive people alive longer, they are more prone to developing progressive cancers associated with aging, which helps explain the increased rates of non-AIDS-defining malignancies reported by many investigators since the advent of HAART. In Dr. Patel’s study, HIV positive individuals were 2–4 times more likely to develop lung cancer, 3–4 times more likely to develop malignant melanoma (a type of skin cancer), and 5–10 times more likely to develop anorectal cancer than the general population. In this cohort, the incidence of other common cancers (breast, colon, prostate) was not significantly different in the HIV positive and HIV negative subjects, but another recent study found a higher rate of prostate cancer among older men with HIV. Because of their higher level of risk, HIV positive individuals should receive regular screening and monitoring to detect developing cancer in its early, more treatable stages.

Non-Hodgkin’s Lymphoma

The incidence of primary CNS lymphoma (lymphoma that originates in the central nervous system, most often the brain) has declined considerably since the early years of the epidemic, but trends for other types of NHL are less clear. Research indicates that people with stronger immune systems are less likely to develop NHL, and HAART therefore has a protective effect. At the same time, as HIV positive people live longer due to effective treatment, there is more time for lymphoma to develop. Since the arrival of HAART, the balance between these two factors has tipped in different directions in different studies.

Data more consistently show that well-controlled HIV disease and higher CD4 cell counts (current or nadir) are associated with lower rates of NHL and better response to treatment (radiation therapy, chemotherapy, or some combination of the two). Individuals with more than 350 CD4 cells/mm³ rarely develop AIDS-related lymphomas, and primary CNS lymphoma typically does not occur above 50 cells/mm³. Individuals not receiving HAART, or whose antiretroviral therapy is failing, are more likely to develop NHL and to experience faster disease progression.

Although early research showed that HIV positive people did not respond as well to NHL therapy, the availability of HAART has reduced or eliminated this disadvantage, in part because it enables the use of full-dose chemotherapy. Christian Hoffmann and colleagues, for example, reported in the July 4, 2003 issue of *AIDS* that good response to antiretroviral therapy independently predicted longer survival in a cohort of 203 participants with AIDS-related lymphoma. While the median length of survival with NHL was about 5–8 months in the pre-HAART era, more recent studies have yielded survival times ranging from 18 to 50 months. (For more on NHL and its treatment, see “Non-Hodgkin’s Lymphoma,” *BETA*, Summer 2003.)

HPV-Associated Cancers

Cancers of the cervix, vulva, anus, and penis are associated with oncogenic strains of human papillomavirus (HPV); nononcogenic strains cause genital and other types of warts. HPV is more prevalent and more aggressive in people with suppressed immune function, and several studies have shown higher rates of abnormal cervical and/or anal cell changes in people with HIV/AIDS. Invasive cervical cancer was added as an AIDS-defining illness in 1993, following pressure from activists who felt the old definition was not sufficiently inclusive of HIV positive women.

Invasive anal cancer is not currently considered an AIDS-defining condition, but many believe it should be.

Effective antiretroviral therapy allows people with HIV to live long enough for HPV disease to progress from abnormal cell morphology (atypical squamous or glandular cells of undetermined significance, ASCUS or AGCUS) to precancerous cell changes (squamous intraepithelial lesions [SIL] or cervical or anal intraepithelial neoplasia [CIN or AIN, respectively]), and finally to invasive cervical or anal cancer—a process that may take up to ten years.

Nevertheless, invasive cervical cancer is not common among HIV positive women in the HAART era. According to a study by L. Stewart Massad, MD, and colleagues reported in the January 2, 2004 issue of *AIDS*, women in the WIHS cohort had a low rate of invasive cervical cancer despite having multiple risk factors. While HIV positive women were more than twice as likely as HIV negative women to have abnormal cervical cell changes (38% vs 17%), just one new case of frank cervical cancer was detected in a woman with HIV during the 1994–2001 observation period, for an incidence rate of 1.2 per 10,000 PY. The researchers concluded that HIV positive women have a low risk for invasive cervical cancer that is “statistically indistinguishable from that in HIV seronegative women and similar to that reported among age- and race-matched women in the general population.”

In contrast, rates of anal cancer appear to be on the rise among HIV positive men who have sex with men (the group at highest risk, although the condition also occurs in women and heterosexual men). For example, Mark Bower, PhD, and colleagues reported at the Bangkok AIDS conference and in the December 15, 2004 issue of *JAIDS* that in a prospective cohort of 8,640 HIV positive individuals, the incidence of invasive anal cancer increased from 35 per 100,000 PY in the pre-HAART era (1984–1995) to 92 per 100,000 PY in the 1996–2003

period—a rate more than 120 times that seen in an age- and sex-matched segment of the general population. Further, comparing the pre- and post-HAART eras, the researchers detected no difference in the overall survival rates of individuals with invasive anal cancer. This is not to say that antiretroviral therapy increases the risk of anal cancer; rather, cancer is more likely to develop as people with HIV live longer. And, unlike with KS and NHL, lower CD4 cell counts and use of HAART are not associated with decreased risk of anal cancer.

Many experts believe the disparity between rates of cervical and anal cancer in people with HIV is at least partly due to differences in medical practice. If detected early—by means of a Pap smear, possibly in conjunction with an HPV DNA test—SIL or intraepithelial neoplasia can be treated before it progresses to frank cancer. Women have long been advised to receive regular Pap smears (at least annually for HIV positive women), followed by colposcopy (examination of the cervix with a lighted magnifying instrument) and treatment (surgery, radiation,

cancer prevention tips

- ◆ Stop smoking
- ◆ HIV positive women should receive cervical Pap smears at least annually
- ◆ HIV positive men who have sex with men should discuss anal Pap screening with their providers
- ◆ Receive screening for breast and colon cancer as recommended based on age

or chemotherapy) if abnormal cells are detected. Since the 1950s the implementation of routine Pap smears has contributed to a 75% reduction in deaths due to cervical cancer in the U.S.

Despite this excellent track record, anal Pap smears are not considered a standard part of regular health monitoring for people with HIV. Researchers are currently studying the benefits of regular anal Pap smears for men who have sex with men. Until more data are available, HIV positive gay and bisexual men should discuss anal Pap screening with their health-care providers.

HAART Risks vs Benefits

Although hepatotoxicity, cardiovascular problems, and other long-term adverse side effects associated with antiretroviral therapy are a serious concern, it is important to emphasize that liver failure, heart attacks, strokes, and other life-threatening or fatal events are quite rare, and certainly less common than fatal OIs during the early years of the epidemic.

In Dr. Reisler's *JAIDS* study, HIV positive people were about twice as likely to experience severe drug-related side effects as AIDS-defining conditions. Looking at data from 2,947 participants in five CPCRA trials collected between 1996 and 2001, the researchers found that 675 subjects (11.4 per 100 PY) experienced severe grade 4 toxicities, compared with 332 (5.6 per 100 PY) who developed AIDS-defining conditions. In the French Aquitaine cohort, 11% of deaths were related to antiretroviral complications including hepatotoxicity and lactic acidosis (a symptom of mitochondrial toxicity associated with certain NRTIs), compared with 10% due to late OIs. While these figures may seem ominous, the higher incidence of drug toxicities relative to AIDS-defining illness is due to the fact that OI rates have declined so sharply, not because severe side effects have

become common.

Few studies have been done comparing the relative risks of antiretroviral therapy and AIDS-defining illness. In one such analysis, Dr. Egger attempted to predict the impact of HAART-related metabolic changes on cardiovascular disease. He estimated that 10–200 people would have to be treated with HAART to produce a single additional case of heart disease. Conversely, because the risk of HIV disease progression is already so low among individuals with CD4 cell counts above 350 cells/mm³ and viral loads below 5,000 copies/mL, 100–200 such people would have to receive HAART in order to prevent one OI. Dr. Egger concluded that the risks and benefits of antiretroviral therapy vary considerably based on individual factors such as age and lifestyle. “While it’s clear that the benefits of HAART outweigh the risks of [heart disease] for many patients,” he said, “there are definitely some patients for whom the reverse may be true.”

Amidst all the sometimes complex and seemingly contradictory data, one fact stands out: HAART has profoundly reduced the rate of OIs and other AIDS-defining conditions, while the absolute incidence of serious treatment-related toxicities remains low. Nevertheless, HIV positive people and their health-care providers should carefully consider a variety of individual characteristics and risk factors when making decisions about anti-HIV therapy (see “On the Level: Making the Decision to Start Therapy,” *BETA*, Summer 2004).

Changes in HIV Management

The shift in emphasis from preventing and treating OIs to coping with side effects of anti-HIV therapy and progressive conditions associated with aging has led to some important changes in the medical management of HIV disease.

It is not yet known how long people will be able to remain on potent antiretroviral drugs, since the longest experience so far is about ten (since the advent of HAART) to 15 years (since the first NRTIs). Concern about the long-term side effects of anti-HIV therapy was part of the motivation for shifting the U.S. federal HIV treatment guidelines from a “hit hard, hit early” strategy to “wait until you need it.” Thus, the recommended CD4 cell threshold for starting therapy in asymptomatic, treatment-naive individuals was reduced from 500 to 350 cells/mm³, while the viral load threshold was raised first from to 20,000 to 55,000 copies/mL, and then this past October to 100,000 copies/mL.

However, as noted previously, it is not yet clear when is the ideal time to start HAART. In the December 1, 2004 issue of *CID*, Dr. Palella, Scott Holmberg, MD, Kenneth Lichtenstein, MD, and Diane Havlir, MD, argued that the move toward later anti-HIV therapy has been based mainly on “sparse and limited cross-sectional data.” Given the availability of newer, less toxic, and more convenient drugs, as well as emerging data indicating that starting HAART with CD4 cell counts above 350 cells/mm³ may be associated with lower mortality, better and more durable immune improvement, less drug-related toxicity, and reduced HIV transmission, the researchers suggested that a reconsideration of the shift away from early treatment is “timely and justified.”

In the same issue, however, two other HIV/AIDS experts, Calvin Cohen, MD, and Brian Boyle, MD, countered that even with newer antiretroviral drugs, there remain major concerns about side effects (such as cardiovascular events, insulin resistance, and bone loss) and drug resistance, and that people who start HAART with low CD4 cell counts still experience “significant immunologic recovery” and ability to control OIs. A large international trial known as SMART is now underway to investigate the relative advantages and

important monitoring tests

- ▶ CD4 cell counts: every 3–6 months
- ▶ HIV viral load: every 3–6 months
- ▶ Blood counts (red blood cells, white blood cells, platelets): every 3–6 months
- ▶ Liver enzyme levels (ALT and AST): before starting HAART and after adding or changing drugs, then every 3–6 months
- ▶ Blood lipid levels (triglycerides and total, LDL, and HDL cholesterol): before starting HAART, 3 months after starting or changing therapy, then every 6–12 months depending on regimen and individual risk factors
- ▶ Cervical Pap smear, with colposcopy if Pap result is abnormal or a woman is at high risk for cervical cancer: at least every year

disadvantages of early vs delayed therapy (see “Open Clinical Trials” on page 49).

Researchers have tried various approaches such as structured treatment interruptions to minimize time on HAART. In recent years, there has been a shift from PIs to NNRTIs as the preferred first-line therapy for asymptomatic individuals with HIV, since NNRTIs are less likely to cause metabolic side effects (although they can cause other types of adverse effects, including hepatotoxicity with nevirapine and psychiatric symptoms with efavirenz [Sustiva]). Perhaps most encouraging, new anti-HIV drugs are being developed that appear less likely to cause metabolic complications, including the new PI atazanavir. Finally, as HAART keeps people alive longer, there is more opportunity to try immune-boosting techniques such as therapeutic vaccines (see “Drug Watch” on next page) and other novel strategies to reconstitute compromised immune function.

As the causes of morbidity and mortality among people with HIV have shifted from rapidly progressing OIs to conditions that develop slowly over the long term, HIV management has had to shift from acute to chronic care. Instead of focusing on providing potent antibiotic and antifungal drugs

to quickly knock out opportunistic pathogens, physicians now must emphasize ongoing monitoring and screening for signs of HAART-related side effects and for conditions that normally occur as people age. Instead of struggling merely to survive, HIV positive people can now endeavor to thrive—aided by good long-term health habits such as quitting smoking, eating a healthy diet, getting ample sleep, and exercising regularly.

A New Definition?

As HIV/AIDS has become a chronic, manageable illness for many people in areas where effective treatment is widely available, it may be time to re-examine the constellation of conditions known as AIDS. In spite of a dramatic drop in mortality due to AIDS-defining illnesses, people with HIV still succumb to so-called “non-AIDS-related conditions” that are, in fact, strongly linked to HIV infection or its treatment. Yet, despite the changing nature of HIV disease, the CDC definition is still based on CD4 cell count and the presence of various OIs. A majority of HIV positive people under competent medical care can keep their CD4 cell counts above 200 cells/mm³ and avoid OIs, unless they are resistant to many drugs. Thus, the current AIDS definition does

not include many people living with HIV disease today.

This definition is not merely academic, since government entitlements and other benefits may be available only to those with a diagnosis of AIDS. It is important that HIV positive people be eligible for coverage of antiretroviral therapy before they develop symptoms, rather than waiting until they are sick enough to fall within the existing AIDS definition. Another avenue is expanding AIDS Drug Assistance Programs (ADAPs) to provide therapies for conditions that are HIV-related but not AIDS-defining, such as cholesterol-lowering medications and antidiabetes drugs. Given the new face of HIV disease, maintaining a good quality of life and attaining near-normal longevity have become the new goals of treatment.

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

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THERAPEUTIC VACCINES: *Ready for Prime (and Boost) Time?*

John
Hawes

Why an HIV vaccine?

We are all waiting for an effective vaccine—one that will prevent HIV infection and relegate AIDS to the same fate as diseases such as smallpox, polio, and diphtheria. At present, this is just wishful thinking because, for many reasons, HIV research has not come close to producing an efficacious vaccine. In the meantime, people continue to become infected with HIV and require lifelong antiretroviral treatment.

The use of antiretroviral therapy has led to dramatic declines in the morbidity and mortality associated with HIV/AIDS, but treatment failure still occurs for a sizable percentage of people within one year of starting therapy (see “Mortality Trends” on page 18). Studies have shown that drug toxicity is the number one reason why people wish to, or need to, stop their antiretroviral therapy. Further, antiretroviral drugs appear incapable of eradicating HIV and cannot completely restore the immune systems of those infected. This has led to the idea of combining immune-based therapies, such as therapeutic vaccines, with current antiretroviral regimens to potentially achieve long-term management of HIV infection. It is also hoped that therapeutic vaccines might extend the benefits of anti-HIV therapy, while minimizing their adverse effects, by allowing for periods of antiretroviral treatment interruption.

Therapeutic vaccines

A therapeutic vaccine is a relatively new immune-based approach that differs from a preventive, or prophylactic, vaccine in that it is not used to prevent infection, but is given to people who already have a disease. One goal of an effective therapeutic vaccine is to strengthen the immune systems of people infected with HIV, enabling their bodies to better fight the virus and lessen their need for antiretroviral therapy. A therapeutic HIV vaccine could theoretically be given during early infection to delay the initiation of antiretroviral therapy and reduce the risk of transmission; during chronic infection to lessen or eliminate the need for antiretroviral therapy; or in cases of advanced disease to slow disease progression and prolong survival.

The idea of a vaccine, whether preventive or therapeutic, is to strengthen the immune response by showing the immune system a disease-causing microbe, or a piece of one, to allow the system to recognize it and build up defenses against it. When a vaccinated person later encounters the same microbe, ideally the body’s defenses will be primed for it and be able to mount a strong and rapid immune response, preventing a harmful infection.

The use of a therapeutic vaccine approach against viruses has been shown to be effective, such as for rabies and hepatitis B virus (HBV), if used soon after infection. Preclinical and animal studies of HIV-like viruses have shown that a therapeutic vaccine approach can be safe—which means “generally well tolerated” and without significant adverse events—and effective, by enhancing immune responses without increasing viral load levels. Most results so far for HIV therapeutic vaccine development in humans have been disappointing, similar to those reported for HIV preventive vaccines. But a recent study showed promise for a whole-killed virus approach different from Remune (see sidebar on page 31) that deserves further investigation.

News from Switzerland

The news from the recent AIDS Vaccine 2004 conference, held August 30–September 1 in Lausanne, was decidedly mixed. There were some positive findings reported from laboratory and animal studies, but not from clinical trials. Two presentations are illustrative of the news from the conference and the state of most HIV vaccine research to date.

One study designed to show the feasibility of using a therapeutic vaccine as part of a treatment interruption strategy in people with chronic HIV infection was reported by George Pavlakis, MD, PhD, of the National Cancer Institute and colleagues. In this study 31 monkeys were infected with SIV (the monkey form of HIV) for up to 70 weeks before being given multidrug antiretroviral therapy. Fifteen of the animals also received a therapeutic vaccine that used specific pieces of viral genetic material to increase the animals’ immune responses while on treatment; the other 16 were not vaccinated. Treatment was

stopped after 20 weeks, then the animals were studied for 7–18 months. The results showed that the monkeys that had received the therapeutic vaccine had a statistically significant reduction in viral load compared with the unvaccinated animals. Although this seems like good news, there is no guarantee that similar results would occur in a human clinical trial.

A case in point was the presentation by Luc Perrin, MD, from the University Hospital in Geneva of results from the international QUEST study. Participants in this trial began antiretroviral therapy relatively soon after infection with HIV. Those people responding to anti-HIV therapy underwent a structured treatment interruption to see whether virological suppression would continue. Some of the subjects stopping therapy received one of two HIV vaccines, an ALVAC canarypox vaccine or Remune, in an attempt to keep them off treatment longer. Unfortunately, the people who received the vaccine and those who did not had similar rates of viral rebound during the treatment interruption. (Both the ALVAC product and Remune have also been studied as preventive vaccines, with little success.)

Prime-boost

One part of the solution to finding a better therapeutic vaccine may be to employ a strategy being used with preventive vaccines: prime-boosting. This strategy was developed because of the lack of protection against HIV seen in previous preventive vaccine research. In this approach, two doses of the vaccine are given: the first one activates (“primes”) the immune system, and the second “boosts” it. The best vaccine candidates to use with prime-boosting are currently being identified, so the results of clinical trials are years away.

Dendritic cells to the rescue?

Meanwhile, researchers from France and Brazil appear to have taken the whole-killed virus approach to a new and far more robust level. In an article published in the December 2004 issue of *Nature Medicine*, Wei Lu and Jean-Marie Andrieu of the Université René Descartes in Paris and colleagues reported that their therapeutic vaccine reduced plasma HIV viral load by a median of 80% after four months in a cohort of 18 Brazilians (16 females, average age of 27 years). At the end of one year, eight subjects had maintained a durable viral load reduction of over 90%. Four of these eight had a viral load between 400 and 900 copies/mL, though none had an undetectable viral load. In addition, HIV-specific CD4 cell counts increased in several subjects, particularly between the first and fourth months of treatment with the vaccine, then generally

returned to baseline levels after one year. The vaccine was also very well tolerated; no adverse events were reported other than increased lymph node size.

These data are striking because none of the study participants were taking antiretroviral therapy before or during the study, all of them had continuously high viral loads for six months before the first of their three vaccine injections, and CD4 cell levels were falling among the group before immunization began.

The unique therapy of Drs. Lu and Andrieu involved using dendritic cells, which are immune cells found in the skin and mucous membranes. Dendritic cells target invading organisms, then carry pieces of these organisms to the lymph nodes, where the body’s more vigorous cell-mediated immune response is activated. HIV normally attacks dendritic cells and ultimately paralyzes the body’s cell-mediated immune response. But in this experiment, dendritic cells were removed from each subject and allowed to process whole, inactivated HIV *in vitro* (in the laboratory). After these dendritic cells were reintroduced into each subject, the results suggested that protective, cell-mediated immune responses against HIV were then properly triggered. This scenario hints at the possibility that the body, with help from a vaccine, could theoretically keep HIV in check without antiretroviral drugs.

While data from this study are tantalizing, future research on this dendritic cell and whole-killed virus approach requires randomized studies involving larger cohorts and a group of control subjects to prove its efficacy.

Pressing ahead

The scientific obstacles to HIV vaccine development are daunting. And a lack of financial incentive for pharmaceutical companies to develop vaccines has been a major economic hindrance. However, there is reason for renewed hope with the G8 countries’ recent endorsement of the formation of the Global HIV Vaccine Enterprise program to speed HIV vaccine development and increase and coordinate vaccine research efforts. Study of immune-based therapies could be energized through such an arrangement.

Although not ready for clinical use, therapeutic vaccines remain a promising avenue of research while investigators look for direction (see “Open Clinical Trials” on page 53). Encouragingly, a recent study of the potential contribution of a therapeutic vaccine to overall HIV care found that even a modestly effective vaccine would result in meaningful increases in life expectancy in people living with HIV.

John Hawes (jhawes7@comcast.net) is a freelance science writer who frequently writes about HIV/AIDS.

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REMUNE: down but not out

The fight against HIV in the arena of vaccine development appears to be still in the first rounds, with no clear winner emerging. One early vaccine candidate still under investigation is Remune, which has been studied both as a preventive vaccine and as a therapeutic vaccine in people already infected with HIV. Like other HIV vaccines, Remune (HIV-1 immunogen, also known as the Salk vaccine, after its inventor, Jonas Salk) was designed to stimulate an infected person's immune system to attack HIV. Remune is made up of inactivated HIV virions (virus particles) that have had their outer envelopes removed. It is an example of a whole-killed virus vaccine, which means that the virus has been modified to make it incapable of infecting cells and replicating. Thus it is potentially safer than some other types of vaccines.

In its initial development as a preventive HIV vaccine, Remune experienced a series of setbacks, including data showing ineffectiveness and legal and financial troubles for its developer, Immune Response Corporation. As a result, this vaccine has become controversial among scientists, with most believing that it does not work and that research efforts would be better directed elsewhere.

Although Remune has not been shown to protect against initial HIV infection, there have been some positive results when it is used as a therapeutic vaccine. Data from a clinical trial presented in 2002 showed that the incidence of antiretroviral failure was reduced by 37% in people who also received treatment with Remune. More recently, the results of a small but well-controlled study at Massachusetts General Hospital showed that Remune restored HIV-specific immune responses in people chronically infected with the virus. More importantly, these responses were similar to anti-HIV immune activity seen in long-term nonprogressors—people who have been HIV positive but asymptomatic for years without treatment. Whether these effects will ultimately have any clinical benefit, however, is not yet known.

The recent clinical findings are certainly welcome news, but Remune might have taken too many body blows in the past for it to be seen as a future vaccine contender. According to the noted AIDS immunologist Bruce Walker, MD, "Remune has now been shown—in the only carefully controlled, double-blinded study ever conducted—to have a positive and measurable biologic effect. Were this any other vaccine but Remune, people would be far more excited." Despite the general lack of enthusiasm, these results are encouraging, and at this point in vaccine research, we should, as Dr. Walker warns, "be testing anything that falls into the category of possible benefit."

Remune may have suffered an early knockdown, but it appears to be pulling itself off the mat. Whether it has the strength to go the distance to win FDA approval is anyone's bet.



Symptoms and Quality of Life in Women

Patrice K.
Nicholas, DNSc, MPH

Symptoms occur across the trajectory of HIV disease and can diminish the quality of life of women living with the virus. Untreated symptoms may also influence medication adherence and lead to complications of HIV and coexisting illnesses. Symptom management can address these concerns. A variety of self-care approaches should be incorporated into any plan of treatment, which ideally should be based on a partnership between the woman with HIV and her health-care providers. This article will address a range of issues concerning symptoms in women with HIV both in the U.S. and worldwide.

Symptoms and Quality of Life

Women with HIV experience a constellation of symptoms, many of which arise early in HIV infection. Symptoms are defined as any perceptible change in the body or its functions. Symptoms of disease are subjective (perceived by the person with the condition), whereas signs of illness are objective (perceived by another person). The experience of the affected individual is the most important index for understanding symptoms and approaching their management.

Symptoms vary according to the stage of HIV disease and any coexisting illnesses. The essential use of highly active antiretroviral therapy (HAART) and side effects related to the drugs also contribute to their occurrence. Symptoms may affect functional status (ability to perform basic activities of daily living) as well as psychological well-being.

Quality of life (satisfaction with the conditions under which one lives) is also influenced by symptoms and is a frequent outcome measure in research. Several studies have shown that HIV symptom control can improve quality of life for women living with the virus. While quality of life is often assessed in HIV clinical trials and in practice

settings, evaluation across the course of disease and in relation to medication regimen is infrequent.

What Symptoms Do Women Experience?

Symptoms in women with HIV may differ from those experienced by HIV positive men. For example, women with lipodystrophy or body fat changes are more likely than men to experience breast enlargement and abdominal fat redistribution, whereas men are more likely to have a dorsocervical fat pad (“buffalo hump”). Women are more likely to have headaches, which are usually poorly identified and poorly managed (see “Headache and HIV” on page 47). Women tend to have more fatigue, which can be related to disease or stress (such as due to childcare), and more abdominal and pelvic complaints that can mimic “normal” female complaints in healthy women. In addition, gynecological symptoms arise early and are often a marker for advancing infection.

Symptoms experienced by HIV positive women in developing countries are remarkably similar to those that affect women in the U.S., although their intensity may be greater. Fatigue, pain, and abdominal problems can be markedly more severe in areas where women lack access to over-the-counter remedies, and where HIV disease tends to advance earlier and progress faster.

Symptoms may be categorized as either physical or psychological; however, the two often overlap. For example, depression in HIV disease is a psychological symptom. Yet experts suggest that brain chemistry and neurotransmitters are linked to depression, so the condition can be considered both a psychological and a physical symptom. Anxiety and sleep disturbances are other examples of symptoms that likely involve both psychological and physical dimensions.

In HIV positive women, psychological symptoms (some of which overlap with physical symptoms) may typically include anxiety, depression, insomnia/sleep disturbances, and changes in body image. Physical symptoms may include diarrhea, nausea and/or vomiting, cough, fever, pain, neuropathy, weight loss, lipodystrophy or body fat changes, rash or other skin problems, and gynecological disorders.

A study published in the September 1, 2004 edition of *Clinical Infectious Diseases* analyzed the prevalence of clinical symptoms associated with antiretroviral therapy in the Women's Interagency HIV Study (WIHS). Michael J. Silverberg, PhD, MPH, and colleagues from Johns Hopkins University in Baltimore reviewed data collected beginning in April 2000 from 1,256 HIV positive women and 364 HIV negative women at several U.S. sites. In the six months before a study visit, 69% of HIV positive women on HAART, 67% of HIV positive women not on HAART, and 49% of HIV negative women reported having at least one clinical symptom. Symptoms reported by the participants included abdominal pain, diarrhea, anorexia, nausea and/or vomiting, fatigue, fever, body fat changes, body image disturbance, dizziness, headache, paresthesias (numbness or tingling sensations), xerostomia (dry mouth), kidney stones, and skin rash.

The researchers found that women who changed their HAART regimens were more likely to experience any symptom—particularly diarrhea, nausea and/or vomiting, body fat changes, muscle pain, and paresthesias—compared with women who remained on stable HAART. The authors concluded that the high prevalence of symptoms in HIV positive women not on therapy and in HIV negative women suggested that antiretroviral drugs were a contributing but not exclusive factor in the development of symptoms.

See the sidebar on page 34 for a comprehensive, though not exhaustive, list of symptoms in women. The list is alphabetical rather than arranged by system (see below).

A Systems Approach

Control of symptoms involves interventions to remove their cause as well as palliation (bringing relief without curing). Symptoms in women are often addressed via a systems approach. Affected body systems include the cardiovascular; respiratory; gastrointestinal; gynecological; genitourinary (genitals and urinary tract); dermatological; ear, nose, and throat; hematological (blood and blood-forming tissues); musculoskeletal; and neurological systems. Psychosocial factors, or the influence of social conditions on mental and physical health, may be considered an additional system in terms of management.

Some systems are more likely to be affected by HIV-related symptoms. For example, the gynecological and dermatological systems are often disturbed in women with HIV. Women may also experience symptoms that are not easily classified using a systems approach. Fatigue, depression, and pain are examples of common symptoms in women with HIV whose etiologies (causes) are often complex and may be related to several body systems.

Self-Assessment and Self-Care

Self-assessment and self-care are often vital for women living with HIV. For many women, self-care is the first or only approach to dealing with symptoms. Because women are frequently caregivers, issues related to childcare may limit their ability to focus on their own HIV-related health needs. Several studies of women with children have examined the difficulties these women face in keeping clinic appointments and addressing their symptom management needs. In addition, stigma remains a major barrier to care for women, particularly in southern Africa and Asia.

Some women use a variety of self-care strategies, including complementary therapies, as well as treatments advised by their health-care providers. In many countries where HIV prevalence rates are over 30%, the sole resource may be home remedies. In resource-limited countries, women may use both antiretroviral medications and traditional remedies to cope with symptoms. Although little evidence exists to support the use of traditional or complementary therapies in HIV/AIDS, more data suggesting their importance for symptom control are becoming available.

Marge Miles, PhD, RN, of the University of North Carolina at Chapel Hill and colleagues developed an intervention to assist African American women with symptom management that included education about self-care and medications, as well as regular home visits. Their study, published in the November/December 2003 issue of *Nursing Research*, showed that women with the intervention had fewer feelings of stigma, higher levels of physical functioning, and less depression and anxiety than women who received standard care.

Symptom Screening and Management

Research-based assessment tools may be helpful not only for routine clinical use by health-care providers, but also for people to comprehensively assess their own symptoms. These self-assessment tools can then be shared with providers to monitor HIV-related symptoms, effects of antiretroviral treatment and complementary therapies, self-care strategies, and progression of illness.

Several valuable symptom assessment and management guidelines exist, including those developed by Lisa Capaldini, MD, of the University of California at San Francisco (UCSF) and published in July 2004 on the HIV InSite web site (see www.hivinsite.org). [Ed. note: Dr. Capaldini is also a member of BETA's Scientific Advisory Committee.]

William Holzemer, PhD, RN, also at UCSF, has developed assessment tools such as the Sign and Symptom Check-List, which covers both signs and symptoms related

symptoms in women with HIV

Anorexia	Fever	Shortness of breath
Anxiety	Forgetfulness	Skin conditions
Cough	Lipodystrophy/ body fat changes	Sleep disturbances
Delirium	Nausea	Swelling of extremities
Dementia-type symptoms	Neuropathy	Vaginal symptoms
Depression	Night sweats	Vomiting
Diarrhea	Oral symptoms	Weight loss
Dizziness	Pain	
Fatigue	Sexual dysfunction	

web sites for symptom assessment and management for women with HIV

- www.aidsnursingucsf.org
- www.hivinsite.org
- <https://statepiaps.jhsph.edu/wihs>
- www.thebody.com/quality.html
- www.thebody.com/Forums/AIDS/SideEffects/index.html

to HIV and their intensity (mild, moderate, or severe). Holzemer's work has led to the development of a web site (www.aidsnursingucsf.org) that includes HIV Self-Care Symptom Management Guidelines, which were produced with UCSF faculty and students, members of the HIV/AIDS Nursing Research Network, and colleagues in four southern African countries (Botswana, Lesotho, South Africa, and Swaziland). This symptom instrument is available in four languages—English, Afrikaans, Sesotho (Lesotho), and Siswati (Swaziland)—so that people living with HIV/AIDS, their formal and informal caregivers, and organizations working with these individuals can manage their illness and related symptoms. Although developed for use with both women and men, the manual addresses many symptoms that occur solely in women (e.g., vaginal symptoms) or are more prevalent in women (e.g., anxiety, depression, fatigue, sleep disturbances).

As a self-care tool for *BETA* readers, a quick reference catalogue of symptoms occurring in women, their causes, and strategies to minimize them is available on the following pages. Also, see the sidebar on this page for a list of web sites providing more information on symptom screening and control in women with HIV.

Summary

Because HIV is an illness that requires ongoing, routine management and evaluation, women must be vigilant about cues to their health. Women often lack a clear understanding of why symptoms arise or the likely course they may take. Some symptoms may be subtle and require careful follow-up and communication between the woman and her providers to track changes over time. For women as well as men, developing a partnership and sharing observations about symptoms with health-care providers is an important aspect of HIV self-care.

Patrice K. Nicholas, DNSc, MPH (pnicholas@mghihp.edu) is professor and chair of Advanced Practice at the Massachusetts General Hospital Institute of Health Professions Graduate Program in Nursing.

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Symptoms, Symptom Etiology, and Self-Care Strategies* for Women with HIV

* Consult with a health-care provider, if possible, when any symptoms develop. Self-care strategies ideally should be used together with approaches recommended by health professionals.

ANXIETY

Causes: worry about HIV infection, anti-HIV medications, mental health issues (including depression), substance use (stimulants)

Self-Care Strategies: relaxation exercises (including meditation, tai chi), anti-anxiety medications

COUGH

Causes: infections (e.g., bacterial pneumonia, *Pneumocystis carinii* pneumonia [PCP], tuberculosis [TB], viruses)

Self-Care Strategies: over-the-counter medications (acetaminophen, cough remedies); drink fluids

DEPRESSION

Causes: brain chemical changes, fatigue, stress, family history of depression, past or current substance use, history of trauma, HIV-related dementia or other organic brain disorders

Self-Care Strategies: psychotherapy/counseling, antidepressant medications, St. John's wort (over-the-counter) [Note: this can interact with anti-HIV medications and should be avoided unless approved by a clinician]; avoid isolation

DIARRHEA

Causes: infections (protozoal, viral,

bacterial), anti-HIV medications (protease inhibitors)

Self-Care Strategies: antidiarrhea medications including over-the-counter agents (acidophilus, Metamucil, Lomotil), acupuncture; drink plenty of fluids and energy drinks (e.g., Gatorade); avoid alcohol, caffeine, fast food, fried foods, dairy products (except yogurt); make dietary changes in consultation with a health-care provider

DIZZINESS

Causes: anemia, dehydration, anti-HIV medications

Self-Care Strategies: if dizzy upon waking, sit up slowly and remain sitting for several minutes before standing up to walk; drink plenty of fluids; eat a healthy diet; consult with a health-care provider about medications and laboratory blood values (hematocrit/hemoglobin)

FATIGUE

Causes: HIV disease progression, anti-HIV medications, anemia, depression, pain, low testosterone, chronic viral hepatitis coinfection

Self-Care Strategies: complementary therapies (e.g., massage, reflexology, acupuncture); get enough sleep every night (8 hours); take frequent rest breaks during the day; exercise in moderation (e.g., walking); eat plenty of fruits, vegetables, and cereals; avoid alcohol, caffeine, substance use, high sugar and high carbohydrate foods; consult with a health-care provider about medications and labora-

tory blood values (hematocrit/hemoglobin)

FEVER

Causes: HIV disease, progression of HIV disease, anti-HIV medications, infection in any of the body systems, coexisting health problems

Self-Care Strategies: drink plenty of fluids without caffeine or alcohol (8–10 glasses of water, juice, ginger ale daily); rest to avoid using up energy; take acetaminophen as directed by a health-care provider; take all anti-HIV drugs and other medications as prescribed; take a full course of antibiotics if prescribed; check temperature with a thermometer and call a health-care provider if higher than 101° F or if elevated for more than 24 hours

FORGETFULNESS

(may be related to early symptoms of delirium or dementia)

Causes: HIV disease, progression of HIV, anti-HIV medications, brain infection (e.g., toxoplasmosis), depression, coexisting health problems

Self-Care Strategies: get enough sleep every night (8 hours); take frequent rest breaks during the day; avoid alcohol and substance use; seek assistance to develop a schedule of daily events; ask for cues and reminders from family/friends; ask family/friends/providers to organize anti-HIV medications and use medication reminders; take all anti-HIV medications but consult with a health-care provider about any other medications

GYNECOLOGICAL SYMPTOMS

Causes: HIV disease, infection (yeast, bacteria, viruses), cervical dysplasia or cancer

Self-Care Strategies: for white, curd-like vaginal discharge use prescription or over-the-counter medications; to avoid vaginal yeast infections eat yogurt and acidophilus each day; wear cotton underwear and change daily; avoid tight clothes and nylon clothing; do not use tampons; do not douche since this disturbs the vaginal flora; use condoms during sex whether or not vaginal symptoms are present; for women with HIV, more careful monitoring to avoid gynecological symptoms is recommended; more frequent Pap smears may be necessary

LIPODYSTROPHY/ BODY FAT CHANGES

(fat loss in the extremities, abdominal fat accumulation, dorsocervical fat pad [buffalo hump], increased breast size, lipomas [benign fat cell tumors], increased prominence of veins)

Causes: unclear; associated with anti-HIV drugs, especially certain PIs and NRTIs (e.g., d4T [stavudine, Zerit], alone or in combination; longer duration of HIV infection; longer duration of anti-HIV drug use

Self-Care Strategies: exercise (especially aerobic); avoid refined carbohydrates in foods and beverages; increase intake of healthy fats (omega-3 and monounsaturated fats); increase fiber intake to at least

25 grams daily and increase soy consumption to reduce cholesterol; increase consumption of beans, fruits, vegetables, nuts, whole grains, and rice

NAUSEA

Causes:

anti-HIV medications, infections, coexisting health problems (e.g., diabetes, alcoholism, chronic hepatitis, reflux esophagitis)

Self-Care Strategies:

medications, both over-the-counter and prescription (e.g., prochlorperazine, metachlopramide); acupuncture; medical marijuana or dronabinol (Marinol), in consultation with a health-care provider; drink enough fluids to avoid dehydration

NEUROPATHY

Causes:

anti-HIV medications (especially d4T, ddI [didanosine, Videx], ddC [zalcitabine, Hivid]), HIV disease, coexisting health problems (e.g., diabetes, alcoholism, chronic viral hepatitis)

Self-Care Strategies:

massage, acupuncture, reflexology, meditation, vitamins, rest, ice (in consultation with a provider), creams/lotions for feet (both over-the-counter and prescription), medications (gabapentin, lamotrigine, tricyclic antidepressants, anti-seizure medications such as phenytoin, carbamazepine, valproate)

NIGHT SWEATS

Causes:

HIV disease, menopause (vasomotor symptoms, hot flashes)

Self-Care Strategies:

avoid extreme temperatures; have a change of clothes and

bed linens available; drink plenty of fluids (8–10 glasses of water daily); take OTC pain reliever after consulting with a health-care provider

ORAL SYMPTOMS/ MOUTH SORES

Causes:

candidiasis (thrush), herpes simplex virus infection, progression of HIV disease

Self-Care Strategies:

eat soft or liquid foods (e.g., mashed potatoes, soup, yogurt, instant breakfast, Ensure, Sustecal); avoid salty, spicy, or acidic food and drinks (e.g., orange juice, pineapple juice, grapefruit juice); use a straw for beverages to minimize liquids' contacting mouth sores

PAIN

Causes:

HIV disease, anti-HIV medications (abdominal pain, neuropathy), infections (bacterial, viral, protozoal), coexisting health problems (e.g., bowel problems, gynecological problems may cause abdominal pain)

Self-Care Strategies:

identify the source and location of the pain if possible; if pain is mild, take OTC pain reliever as directed; if the pain is acute in onset, call a health-care provider

SEXUAL DYSFUNCTION

Causes:

HIV disease and other chronic illnesses, fatigue, depression, body image issues, coexisting health problems (e.g., gynecological problems, vaginal infections, herpes simplex infection)

Self-Care Strategies:

get plenty of rest if decreased libido is due to fatigue; psychotherapy/counseling may improve sexual functioning and body image and limit depression

SHORTNESS OF BREATH

Causes:

respiratory infections (e.g., bacterial pneumonia, viral pneumonia, TB), anemia, fatigue, anti-HIV medications, asthma/emphysema

Self-Care Strategies:

check for fever; watch for respiratory secretions or productive cough (coughing sputum); check breathing rate and notify a health-care provider

SKIN CONDITIONS

Causes:

HIV disease, anti-HIV medications, other medications (e.g., antibiotics), viral infections (e.g., herpes simplex, herpes zoster), bacterial infections (e.g., *Staphylococcus aureus*), yeast infections of skin (under breasts or in groin), Kaposi's sarcoma (KS); sun exposure

Self-Care Strategies:

monitor the skin condition as to size, changes in appearance, drainage from lesions; evaluate whether the skin condition is accompanied by pain or fever; avoid excess sun exposure; use sunscreen as directed; report sudden onset of rash

SLEEP DISTURBANCES

Causes:

HIV disease, anti-HIV medications, anxiety, depression, reduced estrogen level due to menopause, substance use

Self-Care Strategies:

over-the-counter and prescription medications; keep a sleep diary; drink warm milk before bed; avoid large meals before bed; sleep in a darkened room without noise if possible; seek counseling/psychotherapy, with a sleep specialist if possible

SWELLING OF EXTREMITIES

Causes:

HIV disease, lymph system problems

Self-Care Strategies:

rest with legs elevated on pillows, avoid constrictive socks and shoes

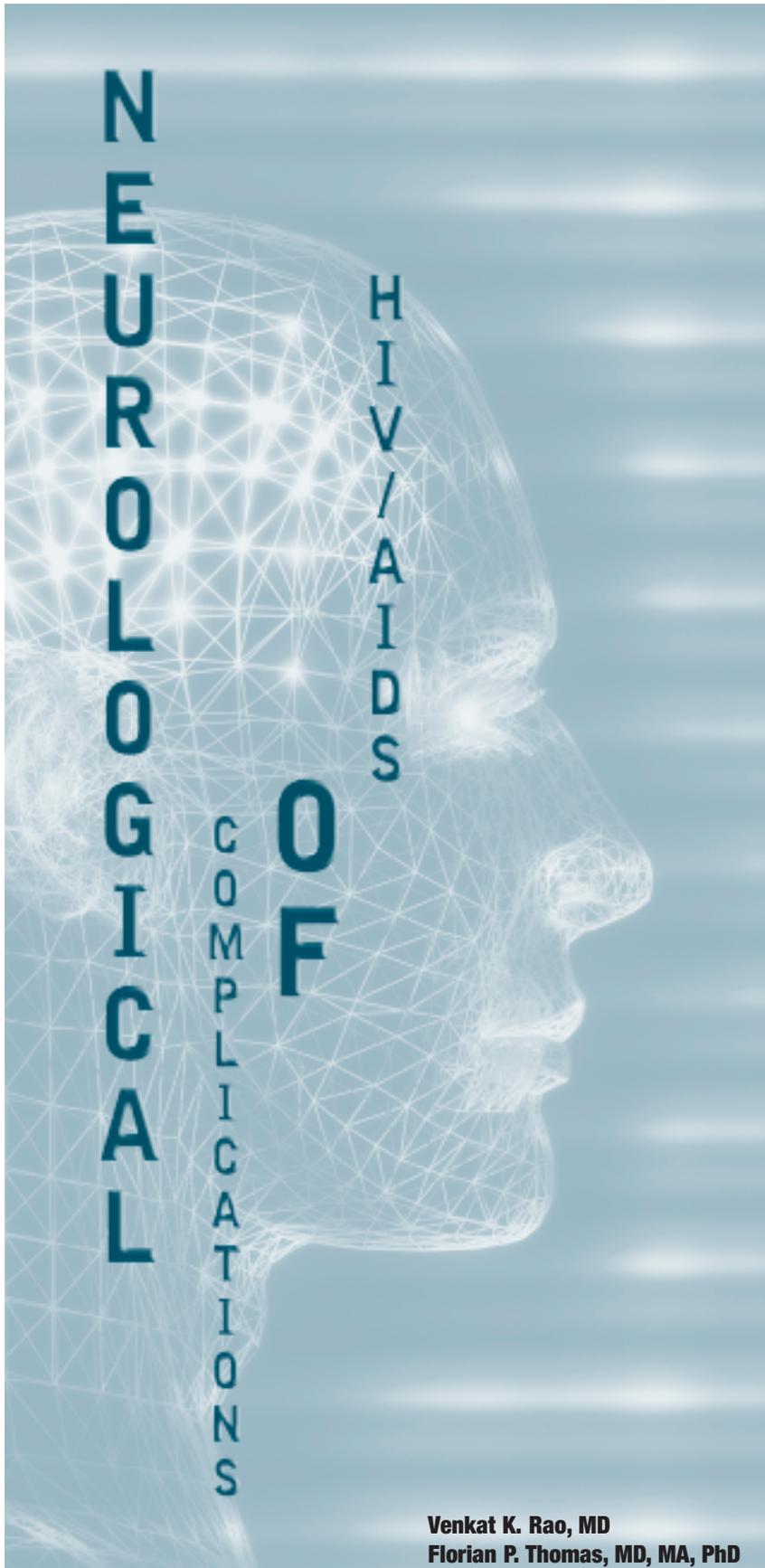
WEIGHT LOSS

Causes:

HIV infection, anti-HIV medications, depression, fatigue, infection (e.g., TB), coexisting health problems (e.g., diabetes, hepatitis)

Self-Care Strategies:

use a scale to keep track of weight every week; eat high-protein, high-calorie foods; eat small, frequent meals (6–8) each day; eat yogurt; drink liquid supplements such as Ensure, Sustecal, or instant breakfast; take vitamin/mineral supplements in consultation with a provider; have high-calorie snacks available between meals; exercise may improve appetite



Venkat K. Rao, MD
Florian P. Thomas, MD, MA, PhD

Neurological complications are common in HIV disease. The spectrum of neurological disorders is broad and involves the central nervous system, or CNS (brain and spinal cord) and the peripheral nervous system, or PNS (nerves outside the brain and spinal cord, and related muscle). Neurological disorders related to HIV often result in reduced quality of life and shortened survival, especially in people with more advanced HIV disease. Nevertheless, some neurological conditions are mild, readily treatable, or reversible. Several have become less common since the introduction of highly active anti-retroviral therapy (HAART). And, despite the fact that many anti-HIV drugs are unable to cross the blood-brain barrier and penetrate the brain, recent data published in the *Journal of Acquired Immune Deficiency Syndromes* support the claim that HAART can improve some neurocognitive functioning.

PATHOPHYSIOLOGY

HIV-related neurological disorders may develop directly from infection with HIV, or indirectly as a result of opportunistic illnesses (OIs) or treatment complications. For example, OIs such as toxoplasmosis often arise from reactivation of previous infections when immune system defenses break down. Viruses that cause progressive multifocal leukoencephalopathy (PML) may be activated by HIV itself. Toxic side effects of certain anti-HIV medications may affect peripheral nerves and muscle.

Different neurological disorders are likely to be seen at different stages of HIV infection (see sidebar on this page). In a first evaluation, the clinician should determine whether clinical features suggest localized (limited to a specific area) or global brain dysfunction, meningitis (inflammation of the membranes covering the brain and spinal cord), spinal cord disease, neuropathy (nerve damage), or myopathy (muscle disease).

The likelihood of a given neurological problem is partly related to the stage of HIV disease as reflected by immune response, viral load level, and CD4 cell count. Levels of cytokines (hormones that coordinate and regulate immune response) have also been implicated.

GENERAL APPROACH

People with HIV often have more than one medical or neurological problem at the same time. A careful history and exam may isolate the diagnosis. Imaging and laboratory studies may help document the diagnosis, and at times identify coexisting illnesses. Neurological diseases are the first manifestation of AIDS in 7–20% of people with HIV and may thus be the AIDS-defining illness.

Due to the complexity of HIV disease and its chronic course, a multidisciplinary approach is important. This may involve general internists, infectious disease and other subspecialists, neurologists, psychiatrists,

physical therapists, and other rehabilitation professionals, including nutritionists.

People with both HIV and hepatitis C virus (HCV) infection may warrant additional neurological observation. In a study published in the March 23, 2004 issue of *Neurology*, Elizabeth Ryan, MD, and colleagues reported that people with advanced HIV disease and HCV coinfection tended to have worse neurocognitive performance and greater impairment of executive functioning (problem solving and other complex use of information) than people with only

advanced HIV disease. Coinfected individuals were also significantly more likely to have HIV-associated cognitive impairment.

CONDITIONS PREDOMINANTLY AFFECTING THE CENTRAL NERVOUS SYSTEM

Many conditions affecting the CNS are associated with HIV infection, and multiple illnesses may be present simultaneously. CNS disorders affect the brain, the spinal cord (but

neurological disorders and stages of HIV disease

Early HIV disease

At the time of seroconversion and in the early stages of HIV disease (CD4 cell levels above 500 cells/mm³) common neurological complications may be undetectable or may include:

- aseptic meningitis
- acute encephalopathy with seizures and confusion
- inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome)
- cranial nerve palsies (e.g., Bell's palsy)
- herpes zoster (shingles)

Moderate to severe immunodeficiency

In moderate to severe immunodeficiency (200–500 CD4 cells/mm³), the following are more likely to be seen:

- cognitive impairment
- distal sensory polyneuropathy (may also appear in early HIV disease)
- myelopathy
- myopathy

Late-stage HIV disease

Illnesses in people with less than 200 CD4 cells/mm³ may include:

- HIV encephalopathy (dementia)
- CNS toxoplasmosis
- cytomegalovirus (CMV) infection
- primary CNS lymphoma
- progressive multifocal leukoencephalopathy (PML)

not the nerves that branch off it, which are part of the PNS), and the membranes covering the brain and spinal cord. Many of these conditions may present either with or without symptoms. The descriptions of conditions below include tests that can be used to make a differential diagnosis.

CNS Toxoplasmosis

Toxoplasmosis, caused by the *Toxoplasma gondii* parasite, is the most common CNS disease associated with AIDS. Usually it is due to reactivation of prior infections in the CNS or elsewhere, but primary infections can also occur. The disease appears during advanced HIV infection when CD4 cell counts are below 200 cells/mm³. Clinical CNS toxoplasmosis is seen in 3–10% of people with AIDS in the U.S.

Onset is over days to weeks. People with CNS toxoplasmosis typically develop headache and fever, followed by impaired thinking and vision, hemiparesis (weakness on one side of the body), and imbalance. Confusion, seizures, meningitis, dementia (deterioration of mental function), and depression may also occur.

A blood test for toxoplasmosis antibodies should be done. A polymerase chain reaction (PCR) assay of the cerebrospinal fluid (CSF) may find *T. gondii* DNA. Magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT, CAT) scan in detecting multiple brain abscesses. A single lesion (tissue abnormality) might suggest a diagnosis of lymphoma instead of toxoplasmosis (see “Primary CNS Lymphoma,” below). A brain biopsy is indicated if there is a single mass lesion and negative serological (blood testing) results, or if there is no response to 14 days of therapy.

Toxoplasmosis is treatable. It is generally responsive to intravenous (IV) antibiotics, and response to therapy is often rapid. Agents of choice are sulfadiazine combined with pyrimethamine and folinic acid. For

people with sulfa intolerance, clindamycin is an alternative. Steroids may be used to reduce associated swelling in the brain.

Ninety-one percent of people treated improve by day 14 of therapy. After the initial regimen is completed, oral maintenance treatment, usually TMP/SMX (Bactrim, Septra), is continued indefinitely to suppress reactivation of the parasite. Prognosis is linked to parallel treatment with HAART to raise the CD4 cell count.

People with HIV who by blood tests appear not to have been exposed to *T. gondii* should avoid eating raw or undercooked meat, particularly pork, lamb, or venison. Fruits and vegetables should be washed, as should one’s hands after contact with raw meat, soil (as after gardening), or a cat’s litter box. Ideally, litter should be changed daily by an HIV negative, nonpregnant person. Household pet feces should always be handled wearing latex gloves. Keeping cats indoors and feeding them only commercial cat food, or well-cooked table food, may reduce their risk of becoming infected with *T. gondii*. Stray cats should be avoided.

Primary Central Nervous System Lymphoma

Lymphoma refers to cancer of the lymph system. It is characterized by the growth of abnormal lymphocytes, or white blood cells (B cells and T cells) that play a part in immune system defenses. HIV-associated primary CNS lymphoma (PCNSL) occurs in the brain, rarely in the spinal cord, and causes brain lesions and changes in mental functioning. In almost all cases, Epstein-Barr virus (EBV) is found in the lymphoma-related lesions or the CSF. EBV’s effect on chronically activated lymphocytes is the probable cause.

PCNSL is associated with CD4 cell counts below 100 cells/mm³. With a prevalence of up to 5% among people with AIDS in the U.S., PCNSL is the second most common mass lesion after toxoplasmosis. Rarely it is the presenting feature of AIDS.

The most common clinical symptoms of PCNSL are impaired cognition, aphasia (loss of ability to use or understand language), hemiparesis, and seizures. Onset is often more subtle, and progression slower, than with toxoplasmosis.

CSF analysis is likely to show pleocytosis (abnormally high number of cells), elevated protein, and malignant-appearing lymphocytes. The presence of EBV in the cerebrospinal fluid is a strong indicator of PCNSL in people with AIDS.

Brain CT or MRI may be useful in suggesting lymphoma by the location and characteristics of tissue changes or uptake of contrast material. Multiple lesions can occur, although less frequently than with toxoplasmosis. MRI spectroscopy (measuring the chemical content of brain lesions) may be easily done during the initial MRI brain scan, and, if certain chemicals are elevated, may suggest lymphoma.

The prognosis for PCNS lymphoma is generally poor. Whole brain radiation therapy (radiotherapy) has been the mainstay of treatment; it provides for a median survival of 2–5 months. Steroids are required for at least 48 hours before radiotherapy to minimize swelling; steroids should be continued throughout the course of treatment. High-dose methotrexate has been used with some success, given as frequently as every week for five cycles. Combining methotrexate and radiotherapy can achieve survival of 1–2 years. Experimental chemotherapy agents include thiotepa (Thioplex) and procarbazine (Matulane). HAART should be continued.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is characterized by widespread demyelinating lesions (loss of the insulating myelin sheath around nerves in the brain and spinal cord) and is caused by the JC papovavirus. Around 90% of the general population have been exposed to this

virus and have antibodies against it. The syndrome of PML occurs almost exclusively in people whose immune systems are suppressed due to HIV or organ transplantation. It is unclear whether PML develops when JC virus in the brain is reactivated or when the virus is reactivated elsewhere in the body, such as the bone marrow, and migrates to the brain. HIV gene products such as the Tat protein may activate the JC virus directly.

PML is usually seen when CD4 cell counts fall below 200 cells/mm³, and it may be an AIDS-defining event. The syndrome likely occurs in less than 4% of AIDS cases where HAART is used.

Onset is usually over weeks to months. The clinical manifestations of PML depend on the areas of the brain affected. Weakness, chiefly hemiparesis, is most common. Other features include behavioral and cognitive problems, aphasia, ataxia (loss of ability to coordinate muscle movement), and cortical blindness (loss of vision due to a brain lesion). Headaches are more rare.

The cerebrospinal fluid is usually normal. The PCR assay is specific and sensitive for the detection of JC virus and can possibly replace a brain biopsy. Both CT and MRI scans may show distinctive tissue destruction just below the cortex, the outer layer of the brain.

PML typically progresses to severe dementia and death over several months. Whether HAART improves survival remains controversial. Survival correlates with suppression of plasma HIV viral load and higher CD4 cell counts. Death may result not from PML but from end-stage immune deficiency. Some positive response has been reported with use of *cidofovir* (Vistide).

Stroke and Hemorrhage

Stroke (“brain attack”) and hemorrhage (spillage of blood from an artery into brain tissue) are major cerebrovascular events; cerebrovascular refers to the blood vessels of the

brain. Causes of stroke and hemorrhage in HIV positive people are numerous and variable.

Hypertension (high blood pressure), blood vessel abnormalities (aneurysms, vein/artery malformations), and cardiovascular disease can lead to brain hemorrhage or stroke, just as in HIV negative people. Hypotension (low blood pressure) can cause stroke in people who are severely ill. Coagulopathies (defective blood clotting) may occur in HIV infection and can lead to stroke or hemorrhage. Thrombotic thrombocytopenic purpura (TTP; characterized by low platelet counts and blood clots) may occur in early phases of HIV disease and may also cause stroke or hemorrhage.

Specific forms of heart disease, particularly accelerated “hardening” of the coronary arteries due to elevated lipids and heart inflammation from various viral infections of the heart muscle, have been implicated in HIV-associated cerebrovascular conditions. Herpes zoster (shingles) over the forehead may cause underlying stroke weeks or months after appearing, and must be considered even in the absence of a rash. Hepatitis C and other infections can also contribute to cerebrovascular problems, such as by impairing blood clotting or leading to abnormal levels of certain blood proteins.

Cocaine and heroin also can cause cerebrovascular problems. Cocaine use may lead to hypertension with hemorrhage, or to blood vessel constriction and stroke caused by lack of blood supply to the brain. Heroin use can cause blood vessel inflammation. Also, nonsoluble contaminants in illicit IV drugs can block blood vessels.

Stroke and hemorrhage are characterized by the abrupt onset of weakness, language problems, or sensory loss. Symptoms often appear on only one side of the body. Imaging studies help differentiate stroke, hemorrhage, infection, and tumors.

Blood tests include complete blood count (CBC) with platelet

count, erythrocyte sedimentation rate (ESR), anticardiolipin antibody and lupus anticoagulant, cryoglobulins, serology for specific infections, syphilis test, blood cultures, coagulation studies including antithrombin III, and protein S and C levels. Analysis of the cerebrospinal fluid may be indicated.

MRI is superior to CT, but both are useful in identifying stroke and hemorrhage. Magnetic resonance angiography (MRA) is useful in detecting blood vessel narrowing. Ultrasound of the carotid arteries (large vessels in the neck that supply blood to the brain) is a less expensive alternative to MRA or CT angiography. A test called transesophageal echocardiography (TEE) may be needed to evaluate the heart for stroke causes, such as dilated cardiomyopathy (failing heart), open channels between the cardiac chambers, or endocarditis (inflammation of the heart valves and lining).

In many cases, treatment parallels that in the HIV negative population. If a stroke is diagnosed within three hours after onset, the person may be a candidate for an infusion of TPA, an agent that dissolves clots and opens blood vessels. TPA is contraindicated (not recommended) in cases of brain hemorrhage. Often lipid-lowering drugs (statins), blood thinners such as warfarin (Coumadin), or antiplatelet agents such as aspirin or clopidogrel (Plavix) are indicated. Specific causes of stroke may require other forms of treatment. Brain hemorrhages occasionally may need to be treated with surgery to remove the mass of blood.

Prognosis after a stroke or brain hemorrhage depends on the size and location of the damage. After a stroke or hemorrhage, the person will recover the most during the initial few weeks, but improvement often continues for months. Inpatient and outpatient rehabilitation is often helpful.

Preventive treatment parallels that in the HIV negative population. Examples include antiplatelet agents or blood thinning drugs. Removal of

plaque from the walls of carotid arteries and newer techniques of endovascular stenting (placing a tube inside a blocked artery) may open and repair vessels.

HIV Encephalopathy

HIV encephalopathy, or AIDS dementia complex (ADC), is one of several neurological conditions that may be caused by HIV itself. Dementia refers to the deterioration of mental function. ADC typically occurs as CD4 cell counts fall below 200 cells/mm³, but mild-to-moderate abnormalities may occur in earlier stages of HIV disease and are known as mild cognitive impairment (MCI). MCI is also associated with chronic hepatitis C and insulin resistance, two conditions that are more common in HIV positive individuals. Fortunately, the frequency of HIV encephalopathy has declined with the use of HAART.

HIV infection may cause ADC-related brain damage indirectly via the production of chemokines, proinflammatory cytokines, nitric oxide, and other neurotoxic factors by both infected and uninfected activated cells. Neurological damage may also occur through the actions of specific HIV proteins, including gp120, gp41, Tat, Nef, Vpr, and Rev, which can be toxic to nerve cells and their dendrites.

People with ADC often present with diminished concentration and memory. Apathy and withdrawal from hobbies or social activities are common, but must be distinguished from depression (see "Overcoming Depression," *BETA*, Winter 2004). Motor problems include imbalance, clumsiness, and weakness. Early signs and symptoms are subtle and may be overlooked. These symptoms may evolve into a severe, global dementia with memory loss and language impairment.

Staging

The following clinical staging of ADC was proposed in 1988:

Stage 0 (normal): Mental and motor functions are normal.

Stage 0.5 (equivocal/subclinical): Symptoms may be absent, minimal, or equivocal, with no impairment of work or performance of activities of daily living (ADL). Mild signs, such as slowed eye or extremity movements, may be present. Gait (manner of walking) and strength are normal.

Stage 1 (mild): The person can perform all but the more demanding aspects of work or ADL but has unequivocal evidence of functional, intellectual, or motor impairment. Signs or symptoms may include diminished performance on memory testing. The person can walk without assistance.

Stage 2 (moderate): The person is ambulatory and able to perform basic activities of self-care but cannot work or maintain the more demanding aspects of daily life.

Stage 3 (severe): The person has major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation). Walking must be assisted (with a walker or personal support); walking is usually slowed and accompanied by clumsiness of arms.

Stage 4 (end stage): The person is bedridden in a nearly vegetative state with urinary and fecal incontinence. Intellectual and social comprehension and output are at a rudimentary level. The person is nearly or absolutely mute.

As is true for any dementing illness, other treatable causes should be sought and corrected if possible. Vitamin B₁₂ (cobalamin) levels should be determined; when B₁₂ is borderline, homocysteine and methylmalonic acid levels are more sensitive. Thyroid stimulating hormone (TSH) and syphilis serology (RPR, VDRL, or MHA-TP) should be checked. CSF analysis serves to exclude other causes of altered mental status. HIV in the CSF frequently is detected by PCR, and may suggest a need to alter

HAART. Imaging studies may reveal progressive brain atrophy (shrinkage) or characteristic white matter changes. Electroencephalography (EEG; recording the electrical activity of the brain) shows generalized slowing in the later stages of ADC. Positron emission tomography (PET) scanning is sensitive for dementia, but not specific for HIV-related dementia.

In general, depression and metabolic causes of cognitive decline, such as other infections, vitamin deficiencies, thyroid dysfunction, and liver and renal dysfunction, should be aggressively corrected. Antiretroviral agents protect against ADC and can induce remission, but when treatment fails and viral load rebound occurs, cognitive function again deteriorates. If ADC develops during treatment with HAART, additional or alternative agents should be tried. Neuroprotective therapies or global memory enhancing agents such as memantine (Namenda) or donepezil (Aricept) may be useful in some individuals.

Close follow-up is needed because the person's cognitive impairment may progress to dementia, or the person may develop seizures or psychosis (a severe mental disorder often characterized by delusions or hallucinations). Also, people with ADC must often take multiple medications, many of which can affect thinking and memory and thus make the symptoms of ADC worse.

Cytomegalovirus Encephalitis

Cytomegalovirus (CMV) is a herpesvirus that often infects healthy people without causing symptoms. But in people with compromised immune systems, typically those with less than 50 cells/mm³, CMV may cause serious disease.

CMV infection of the brain, spinal cord, meninges, or nerve roots can lead to neurological problems such as encephalitis (inflammation of the brain), myelitis (inflammation of the spinal cord), retinitis (inflammation of the retina of the eye), polyradiculitis

(inflammation of the spinal nerve roots), peripheral neuropathy, or mononeuritis multiplex (see “Mononeuritis Multiplex,” below). Some 20% of people with CD4 cell counts below 100 cells/mm³ harbor CMV in different organs and suffer from colitis (inflammation of the large intestine), esophagitis (inflammation of the esophagus), or retinitis. Autopsy studies reveal CMV in the CNS in 5–40% of people with AIDS, and often the diagnosis was not made during life.

People with HIV-associated CMV encephalitis may present with confusion and cognitive decline. The condition can arise suddenly with rapid progression of altered mental status and cognitive deterioration. Changes might also develop more slowly and be indistinguishable from HIV encephalopathy. CMV encephalitis may occur together with previously known or newly diagnosed CMV-related inflammations or neuropathy.

Typical CSF findings include low-to-normal glucose, normal-to-high protein, and increased numbers of white blood cells. CMV can be detected by PCR. A CT or MRI scan may show nonspecific abnormalities, but a contrast enhanced MRI may strongly suggest the diagnosis. Mass lesions due to CMV are rare.

Untreated CMV encephalitis is almost always fatal and causes death in days to weeks. Anti-CMV drugs must be started immediately, often based on a suspected rather than proven diagnosis. Treatment relies on two drugs, ganciclovir (Cytovene) and foscarnet (Foscavir), used alone or in combination when monotherapy fails. Lifelong maintenance treatment is often necessary. More than 50% of those who take anti-CMV agents stabilize or improve, but the overall prognosis is determined by the stage of HIV disease.

Cryptococcosis

Cryptococcosis, caused by the *Cryptococcus neoformans* fungus, is the most common CNS fungal infection in

people with AIDS. It develops when CD4 cell counts fall below 100 cells/mm³. Cryptococcosis presents as meningitis, a space-occupying lesion, or meningoencephalitis (inflammation of the meninges and brain). It typically reaches the CNS from the lungs. It can also affect skin, bone, and the genitourinary tract.

The nonspecific nature of early features may lead to significant treatment delay, so a high level of suspicion is warranted. Early symptoms and signs include headache, fever, malaise, nausea and vomiting, stiff neck, double vision, altered mental status with drowsiness, and photophobia (abnormal sensitivity to light). Hydrocephalus must be suspected with new-onset impaired consciousness; motor signs such as a stiff, shuffling gait; nausea; vomiting; or visual impairment. Hydrocephalus is a blockage of the normal flow of CSF in and around the brain; it may occur with cryptococcal meningitis and may cause worsening headache and gait imbalance. Occasionally, the spinal cord may be involved, leading to radicular (nerve root) pain, stiffness or spasticity, limb weakness, and problems with bowel and bladder control.

CSF appearance on examination may be clear or cloudy, and often shows mild abnormalities in cell count or protein levels. *C. neoformans* is found in nearly all CSF samples. MRI is the preferred brain scan to reveal meningeal inflammation or cryptococcal abscesses.

Untreated cryptococcal CNS infections are fatal. Treatment relies on amphotericin B (Fungizone), which may be combined with flucytosine (Ancobon). An alternative for less severe cases is fluconazole (Diflucan), which is also the drug of choice for long-term prophylaxis (preventive therapy). Amphotericin B is an alternative maintenance therapy for people who relapse on fluconazole or do not tolerate it.

Hydrocephalus can occur at times and requires a ventriculoperitoneal

shunt (surgical drain of spinal fluid). Visual loss can be addressed by optic nerve surgery.

Several studies report mortality rates of 17–20%, but with aggressive therapy this may drop to 6%. A minority of people die within the first six weeks after diagnosis despite treatment. Relapse rates without prophylaxis range from 15% to 27%; this is reduced to 0–7% with prophylaxis.

Meningitis

Meningitis is an inflammation of the meninges, the membranes surrounding the brain and spinal cord. HIV positive people are at higher risk than the general population of developing bacterial or viral meningitis, which may be caused by HIV itself. Cryptococcal meningitis, caused by the *C. neoformans* fungus, is also common. More uncommon CNS infections are due to the *Listeria monocytogenes* bacterium, coccidiomycosis (valley fever), histoplasmosis (caused by the *Histoplasma capsulatum* fungus), syphilis, and tuberculosis. Meningitis due to CMV or fungal infection occurs typically with very low CD4 cell counts. Rarely, lymphoma can present as meningitis. Allergic reactions are more common in people with HIV, and chemical meningitis associated with medications such as pegylated interferon, and even ibuprofen, has been described.

Individuals with meningitis present with malaise (vague body discomfort), fever, stiff neck, photophobia, and headache. Less common are cranial neuropathies (one-sided facial weakness or double vision), confusion, drowsiness, and personality changes.

HIV invades the brain early and may cause meningitis within days to weeks after HIV infection. Chronic meningitis, or episodes of acute (rapid onset) meningitis for which no cause is found, can occur anytime during the course of HIV disease. These episodes may reflect HIV itself, or may occur with outbreaks of herpes

simplex type I (cold sores) or type II (genital skin eruptions).

CT and MRI brain scans may show inflammatory changes surrounding the brain. CSF analysis often gives results that identify the type of meningitis and organism involved.

Treatment and prognosis vary by the specific cause of meningitis, severity at presentation, delay from symptom onset to treatment, and status of immunosuppression. For treatment of meningitis due to CMV or cryptococcal infection, see the “Cytomegalovirus Encephalitis” and “Cryptococcosis” sections, above.

Neurosyphilis

Syphilis is a sexually transmitted infection caused by the spiral-shaped *Treponema pallidum* bacterium.

T. pallidum gains access to the body through tiny abrasions of the skin or mucous membranes. This organism may invade the CNS a few months after initial infection. Some studies suggest that syphilis may follow a more aggressive course in people with HIV.

Syphilis in people with HIV may proceed more rapidly than usual from the primary stage (skin chancres, or lesions, appearing about 21 days after infection) to secondary (skin rash) and tertiary (infection of different organs, including the brain) syphilis as early as two months after exposure.

A person with syphilis may not recall the painless skin chancres and may present with secondary syphilis, with a dusky red, roundish rash (slightly raised with slightly peeling overlying skin) on the palms of the hands. At this point, 24% of people will already have CSF abnormalities. This early invasion of the brain, combined with a delayed or absent blood test for syphilis, increases the risk of delayed or missed syphilis diagnosis and advancement to tertiary syphilis.

Tertiary syphilis may present as hearing loss, dizziness or vertigo, headache, failing vision, cognitive impairment, personality changes,

peripheral polyneuropathy, gait imbalance, seizures, or stroke.

The standard test for neurosyphilis is a VDRL (“syphilis”) test of the cerebrospinal fluid. A positive CSF VDRL points to a neurosyphilis diagnosis. However, a negative CSF VDRL cannot exclude neurosyphilis, and a high clinical suspicion of the condition may be the ultimate test. A negative syphilis antibody test of the CSF (for example, using the FTA-ABS assay) excludes neurosyphilis.

The VDRL or RPR test of the blood may be negative in 25% of people with neurosyphilis. Syphilis antibody blood tests such as MHA-TP or FTA-ABS will remain positive with neurosyphilis and should be added to the blood VDRL test.

CSF cell count, glucose, and protein levels may be normal in 30% of cases, and, again, clinical suspicion of syphilis may overrule negative or normal tests.

The choice of antibiotic depends on the stage of syphilis and follows general guidelines. Most common are different forms of penicillin. While people with HIV with neurosyphilis respond to antibiotics, they are less likely to have serological improvement than HIV negative individuals. HIV-associated neurosyphilis may be more difficult to treat and more aggressive, likely due to impaired immune responses to *T. pallidum*.

Tuberculosis Meningitis

Tuberculosis (TB) is a bacterial disease caused by *Mycobacterium tuberculosis*, which can be suspended in tiny droplets in the air and transmitted person to person by inhalation. Worldwide, TB is the most common OI associated with late-stage HIV disease, when CD4 cell counts are very low. Neurological complications are often present; tuberculosis meningitis is the most common manifestation.

Tuberculosis affecting the brain may cause persistent headache, fever, confusion, hemiparesis, seizures, stiff neck, double vision, or hearing loss. Hydrocephalus associated with

tuberculosis may lead to drowsiness or stupor and, later, coma. Spinal cord damage can occur if the vertebrae (bones that encase the spinal cord) are infiltrated by TB, also known as Pott’s disease, or as a result of abscesses inside or outside the spinal cord.

CSF studies are useful, especially DNA PCR probes for *M. tuberculosis*. MRI brain scan may reveal thickening of the coverings of the brain, abscesses, stroke, and enlarged ventricles (an indication of hydrocephalus).

Triple antibiotic therapy—isoniazid, rifampin (Rifadin), and pyrazinamide—for 12–24 months is required. It is important that all doses be taken as directed. In cases of drug-resistant TB, a fourth drug (ethionamide [Trecator]) should be added to the regimen above. HAART should be continued. Significant interactions can occur between rifampin and protease inhibitors (PIs), so an alternative anti-TB drug may be necessary.

Tuberculomas (tumor-like masses) can develop in people with HIV. Combination medications are used initially, unless the tuberculoma is causing a critical brain swelling or spinal cord paralysis.

Myelopathy

HIV-associated myelopathy (spinal cord disease), or vacuolar myelopathy, is the most common chronic spinal cord condition associated with late-stage HIV disease, when CD4 cell counts are very low. Myelopathy often presents together with ADC, peripheral neuropathies, and OIs or malignancies. The secretion of neurotoxic factors by HIV-infected blood cells or the expression of HIV gene products in certain cells of the nervous system may contribute to this condition. Impaired ability to use vitamin B₁₂ for myelin maintenance in the spinal cord may be a contributing factor.

People with HIV-associated myelopathy present with chronic progressive and painless leg weakness,

stiffness, and imbalance. Sensory loss may be minor. Bowel and bladder control are affected only if the legs are severely weak.

CSF examination is usually normal. CSF studies should include DNA PCR tests for CMV and herpes zoster. CSF cytology (cell analysis) should be done to exclude lymphoma. MRI spine scan should be done to exclude vertebral disc disease. It may also reveal changes specific to HIV myelopathy. Vitamin B₁₂ deficiency occurs more frequently in people with HIV and may cause spinal cord and peripheral nerve damage.

Once treatable causes of myelopathy have been excluded, prognosis is poor, options are limited, and care is primarily supportive. People with the condition may improve after starting HAART. To stabilize spinal cord damage, maximally potent HAART is required. L-methionine (also known as SAMe, a common dietary supplement) is an experimental treatment.

CONDITIONS PREDOMINANTLY AFFECTING THE PERIPHERAL NERVOUS SYSTEM

A wide spectrum of PNS-related conditions is associated with HIV infection, and many people have more than one specific diagnosis. PNS disorders affect the spinal nerve roots where the nerves exit the spinal cord, and the route along the peripheral nerves down the arms and legs. HIV also affects muscles. HIV-associated complications in the PNS and muscles are clinically apparent in over 30% of people with HIV. Because they may be subclinical (without symptoms), neuromuscular abnormalities are often detected by electromyography and nerve conduction studies or histological studies, as described below.

Distal Sensory Polyneuropathy

Distal sensory polyneuropathy (DSP), or damage to sensory nerves in

the extremities (feet and hands), is the most common type of HIV-associated neuropathy. Nerves may be injured directly by HIV or by HIV-induced macrophages that secrete neurotoxic substances. DSP may also be caused by nutritional and vitamin imbalances or drug toxicity, especially use of d4T (stavudine, Zerit), ddI (didanosine, Videx), or ddC (zalcitabine, Hivid).

DSP may occur at any stage of HIV disease. People with DSP may complain of tingling, burning, or shooting pain on the soles of their feet. The pain slowly advances to the top of the foot and then may envelope the lower leg. As the DSP creeps up the leg to the knee, the fingertips and hands typically become affected. Bladder and bowel control may be affected, as well as the ability to achieve an erection in men.

Blood tests for diabetes mellitus, thyroid dysfunction, vitamin B₁₂ level, syphilis, and many others should be done to exclude other treatable causes of neuropathy. CSF studies are useful if CMV or syphilis is suspected.

Electromyography and nerve conduction studies may reveal damage to axons (long nerve fibers that conduct impulses away from nerve cells) or to the insulating myelin sheath around axons. Electromyography refers to the insertion of small needles into affected muscles to monitor muscle and nerve function; nerve conduction studies refer to the placing of electrodes on the skin over nerves and using small pulses of electrical current to monitor nerve response.

It may be necessary for a person with DSP to stop taking d4T, ddI, or ddC. Vitamin B₁₂ supplementation by mouth is needed if there is a deficiency. Intake of vitamin B₆ (pyridoxine) should be reduced, if necessary, as more than 50 mg per day may cause polyneuropathy.

Treatment of symptoms may include local ointments (capsaicin, Aspercream), antidepressant medications (amitriptyline [Elavil]), or

antiepileptic medications (gabapentin [Neurontin], lamotrigine [Lamictal], carbamazepine [Tegretol]). Duloxetine (Cymbalta; an SSRI antidepressant) is FDA approved for painful diabetic polyneuropathy, and is currently being used for HIV-associated painful polyneuropathy. Pregabalin (Lyrica; an antiepileptic drug) is under FDA review. Drugs should be chosen that are unlikely to interact with or influence the effectiveness of anti-HIV drugs. Lidoderm patches may provide partial pain relief without any systemic side effects and can be combined with oral drugs. For trials of therapies for neuropathy pain, see "Open Clinical Trials" on pages 51–52.

Inflammatory Demyelinating Polyneuropathy

HIV infection is an important cause of inflammatory demyelinating polyneuropathy (IDP), or inflammation of the myelin sheath that surrounds the spinal and peripheral nerves.

The acute form of IDP (AIDP), also known as Guillain-Barré syndrome (GBS), is characterized by rapid onset and progression over hours to weeks. The chronic form (CIDP) has slower onset and progression over weeks to months, sometimes with a relapsing course. Both forms are autoimmune conditions in which the immune system attacks nerves. GBS can be triggered by infections or immunizations, and is more often seen at the time of HIV seroconversion, but can occur at any stage of HIV infection, as can the chronic form of IDP.

IDP causes varying degrees of weakness and sensory loss, which can develop in the limbs. Nerves around the head may also be affected and cause symptoms such as facial weakness and double vision. Other features may include pain and diminished reflex responses. Sometimes people with IDP have difficulty with urination and bowel movements, and occasionally respiratory paralysis,

irregular heartbeat, and dangerously high or low blood pressure can ensue.

CSF studies will show significantly elevated protein during the first few days or weeks of the syndrome. Often the cell count is elevated as well in both acute and chronic IDP associated with HIV infection, whereas GBS in people without HIV is characterized by normal cell counts. Repeated lumbar punctures (spinal taps; inserting a needle into the spinal column to remove cerebrospinal fluid) may be needed. Electromyography and nerve conduction studies may be useful in diagnosing acute or chronic IDP.

Treatment and response rates are similar to those seen in the HIV negative population. Intravenous immunoglobulin (IVIG), a highly concentrated antibody infusion from many pooled blood donations, is the mainstay of therapy. Plasma exchange, or plasmapheresis, may be helpful; in this procedure antibodies are removed from the blood. Chronic IDP may also require corticosteroids such as prednisone.

Mononeuritis Multiplex

Mononeuritis multiplex (MM) is a usually painful condition that involves isolated nerves over the arms, legs, or trunk. The nerves are affected asymmetrically. The involvement of more than two nerves is generally seen in people with advanced HIV, and may be caused by CMV.

People with MM typically complain of burning or shooting pain down an arm, then, even as it is resolving, another burning pain will emerge over another nerve pathway down a different arm or leg. Weakness in the distribution of specific nerves is common. Nerves can be affected in the head and the body.

Blood tests for diabetes mellitus and immune abnormalities should be done. Electromyography and nerve conduction studies may be useful in making the diagnosis. CSF studies are usually nonspecific, but if done, DNA PCR for herpes zoster, herpes

simplex I and II, and CMV may be useful. Nerve biopsy may also be useful if a pathology lab familiar with the procedure is available.

Mononeuritis multiplex occurring early in HIV infection may resolve with HAART. IVIG or plasma exchange should be considered in early or late HIV stages. People with late-stage HIV disease may require anti-CMV medications (ganciclovir, foscarnet).

Polyradiculopathy

Polyradiculopathy is damage to the nerve roots where the nerves exit the spinal cord to form peripheral nerves. Polyradiculopathy may be caused by CMV, or less likely by lymphoma. It may also be idiopathic (of unknown origin). CMV polyradiculopathy occurs with very low CD4 cell counts, and CMV may already be present at other sites, such as the retina.

Rapidly progressive ascending numbness, pain, and weakness affecting the legs, and later occasionally also the arms, is characteristic of the CMV form. Early bowel and bladder control problems may suggest the syndrome. A more benign, slower clinical progression characterizes the idiopathic form.

CSF analysis may show elevated protein and white blood cells, and decreased glucose. A PCR test of the CSF is useful to identify or exclude CMV. MRI of the spinal cord may be needed to exclude structural compression of the spinal cord, such as from a large disc herniation or tumor, or spinal cord lesions due to lymphoma, syphilis, Kaposi's sarcoma (KS), or toxoplasmosis. Electromyography and nerve conduction studies help differentiate polyradiculopathy from other rapidly progressive neuropathies such as Guillain-Barré syndrome.

CMV polyradiculopathy is rapidly fatal without therapy. Treatment with foscarnet or ganciclovir may improve or stabilize the condition. HAART also may be useful. The idiopathic form

may improve spontaneously without treatment.

Myopathy

Myopathy refers to many forms of muscle disease. HIV-associated myopathies fall into several categories. Some are caused by drug toxicity, for instance, due to cholesterol lowering drugs (statins), ddI, or AZT (zidovudine, Retrovir). Others are caused by a variety of bacterial, viral, and other infections. Still others, such as polymyositis (inflammatory disease of muscles), are due to an abnormal immune response. HIV wasting syndrome may result from HIV infection itself.

Progressive muscle weakness is the typical presentation, with the speed of progression depending on the cause.

The serum creatine kinase (CK) level is often increased but may be normal. Electromyography, nerve conduction studies, and muscle biopsy are often indicated. Imaging studies (CT, MRI, Gallium-67 scan, ultrasound) are helpful when certain infections are suspected.

When medications are the likely cause, they may need to be stopped or replaced. Muscle infections are treated with drugs specific to the responsible bacterium, virus, or other infectious agent. When inflammation results from an overactive immune system, corticosteroids may be a treatment option.

CONCLUSION

HIV is associated with a range of neurological problems. Fortunately, many of these conditions have become rarer with the use of HAART and the subsequent improvements in health for many HIV positive people. Access to a clinician with experience in neurological disorders specific to HIV disease is essential for the prevention, early diagnosis, and treatment of neurological conditions in this population.

GLOSSARY

BIOPSY:

the removal of a small sample of cells or tissue for microscopic examination and/or culture, typically for diagnostic purposes.

CEREBROSPINAL FLUID (CSF):

a clear fluid that circulates around and through the brain and spinal cord.

COMPUTED TOMOGRAPHY SCAN (CT SCAN, CAT SCAN):

a method of visualizing the bones and tissues of the body using x-rays.

DEMENTIA:

the deterioration of mental function.

DEMYELINATION:

the loss of the lipid myelin sheath that surrounds nerve cells and is necessary for proper transmission of neural impulses.

DIFFERENTIAL DIAGNOSIS:

a method of diagnosis that involves determining which of a variety of possible conditions is the probable cause of an individual's symptoms, often by a process of elimination.

HEMIPARESIS:

weakness on one side of the body.

HERPES ZOSTER (SHINGLES):

a condition characterized by painful blisters caused by reactivation of varicella-zoster virus (VZV). Blisters typically appear in a linear distribution on the skin following nerve pathways; outbreaks occur more frequently and may be more severe in immunocompromised individuals.

HYDROCEPHALUS:

a blockage of the normal flow of cerebrospinal fluid in and around the brain.

LESION:

any abnormal tissue change caused by disease or injury.

MAGNETIC RESONANCE IMAGING (MRI):

a sensitive, noninvasive method for viewing organs and tissues of the body using a strong magnetic field.

MYELIN:

a white, fatty substance that forms a sheath around nerve fibers and provides insulation necessary for proper transmission of neural impulses.

PALSY:

muscle paralysis.

PATHOPHYSIOLOGY:

changes in function associated with disease.

PLATELET:

a type of blood cell that facilitates normal blood clotting.

POLYMERASE CHAIN REACTION (PCR) ASSAY:

a highly sensitive test that can detect small amounts of genetic material in a blood or tissue sample.

POSITRON EMISSION TOMOGRAPHY (PET) SCAN:

an imaging method in which a radioactive substance is injected into the bloodstream and a scanner is used to measure cerebral blood flow in different parts of the brain.

PROGNOSIS:

a forecast of the probable course or outcome of a disease.

SEROCONVERSION:

the change in a person's blood antibody status from negative to positive; development of antibodies against a microorganism.

ULTRASOUND:

an imaging technology using high-frequency sound waves.

Venkat K. Rao, MD

(kit2savi@yahoo.com) is a staff physician in the Department of Neurology at Saint Louis University Health Sciences Center.

Florian P. Thomas, MD, MA, PhD

(thomasfp@slu.edu) is an associate professor in the Department of Neurology at Saint Louis University Health Sciences Center.

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headache and HIV

Gregory
Pauxtis, MD

Headaches are common in the general population. People with HIV may experience headaches at the time of seroconversion, while using medications to treat HIV or viral hepatitis, and in late-stage HIV disease with CD4 cell counts below 100 cells/mm³.

People with HIV who experience headaches are often concerned that an infection of the air sinuses or the brain has been overlooked. Like their HIV negative counterparts, individuals with HIV may also be concerned that allergy, vision problems, or cervical (neck) spine disease is the cause of their headaches.

With a careful medical history and exam, at times followed by an MRI brain scan, infection and tumors can be excluded as the cause. A CSF exam may be done to exclude infection or inflammation due to medications, such as pegylated interferon-alpha (Pegasys, Peg-Intron) for hepatitis C. After these likely causes have been excluded, the HIV positive person will generally be diagnosed with a vascular headache, especially the common migraine, as in the general population. Migraine refers to a severe recurring headache, typically on one side of the head, or more broadly defined as any severe headache associated with nausea or photophobia (abnormal sensitivity to light) and phonophobia (abnormal sensitivity to sound).

Headaches in people with HIV might have several origins. Migraine headaches are generally believed to arise from the dilation (expansion) of arteries in the brain and scalp and the release of nerve chemicals that cause pain. Some headaches may reflect chemical pathway dysfunction of the glial cells that support neurons. Michael Moskowitz, MD, of Harvard Medical School reports that when macrophages that line the blood vessels in the brain become activated or degranulate (release chemical messengers from vesicles called lysosomes), inflammation develops around the blood vessels, resulting in headaches. In HIV disease, macrophage dysfunction and activation are associated with abnormal levels of cytokines (hormones that coordinate and regulate immune response).

Headaches can be triggered by various conditions, including sleep irregularities, stress, tobacco smoke, bright light, noise, perfumes or odors, fasting, eating certain foods, or hormonal imbalances, such as excessive estrogen from birth control pills or due to metabolism of excessive testosterone supplements. Some people are likely to be genetically predisposed to migraines, and females are more likely to experience them than males.

Migraine treatments are divided into those used for preventing headaches and those used for stopping the headaches as they recur. People with HIV should consult with a clinician before taking any headache medication. Headache prevention therapies include blood pressure medications (calcium channel blockers, or beta blockers such as propranolol [Inderal]) and tricyclic antidepressants (such as amitriptyline [Elavil]). A combination of both blood pressure drugs and tricyclic antidepressants is more effective than either drug used alone. Other preventive medications include antiepileptic drugs, such as valproic acid (Depakote) or topiramate (Topamax). Topiramate may be preferred since it will not interfere with anti-HIV drugs that depend on liver metabolism. Side effects from topiramate may be reduced by taking the entire headache preventive dosage (100 mg) at night only. Vitamin B₂ (riboflavin) 400 mg per day is also reported to be effective in preventing headache.

Therapies that stop headaches as they recur include triptan drugs such as sumatriptan (Imitrex). Drugs known as ergot alkaloids, such as ergotamine tartrate (Ergomar) and dihydroergotamine (Migranal), should be avoided due to increased side effects with HAART. Over-the-counter analgesics (pain relievers), such as acetaminophen (e.g., Tylenol), aspirin, ibuprofen (e.g., Advil), and naproxen (e.g., Aleve), are helpful in stopping migraine headaches. However, overuse may lead to analgesic rebound headaches.

Smoking cessation, adequate sleep, acupuncture, and biofeedback (the use of monitoring devices to train a person to consciously control involuntary functions, such as heart rate) might also be helpful.



OPEN CLINICAL TRIALS FOR HIV/AIDS TREATMENTS

Below is a partial listing of currently enrolling U.S. clinical trials gathered from various sources. As of August 2004, **TrialSearch**—an extensive online database of clinical trials related to HIV/AIDS—has been operated by the **AIDS Community Research Initiative of America (ACRIA)**. The University of California at San Francisco's **HIV InSite** web site (which formerly offered TrialSearch) now features **TrialScope**, a database of organizations that conduct HIV/AIDS-related research.

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

The National Center for Complementary and Alternative Medicine (NCCAM) provides a listing of alternative therapy studies for conditions related to HIV or its treatment. **The HIV Vaccine Trials Network (HVTN)** is an international collaboration testing preventive vaccines against HIV/AIDS. **Community Programs for Clinical Research on AIDS (CPCRA)** is a nationwide network that conducts community-based clinical trials. In addition to hosting TrialSearch, ACRIA also provides a listing of trials mostly in the mid-Atlantic region (New York, New Jersey, Connecticut, and Pennsylvania).

The Body web site has created a new database of prospective clinical trial volunteers. The service collects information about participants' city, age, viral load, CD4 cell count, current and past anti-HIV therapy, and health status. Researchers can request information about prospective subjects, who will be contacted if they meet a trial's enrollment criteria. The application form is available at <http://ssl.thebody.com/submit/?/clinicaltrials/general.html>.

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

ACRIA: www.acria.org

AIDSinfo: www.aidsinfo.nih.gov/clinical_trials

CenterWatch: www.centerwatch.com

ClinicalTrials.gov: www.clinicaltrials.gov

CPCRA: www.cpcra.org

HIV Vaccine Trials Network: www.hvtn.org

NCCAM: www.nccam.nih.gov/clinicaltrials/hiv.htm

TrialScope: www.hivinsite.org/tscope

TrialSearch: www.acria.org/clinical_trials/index.html

Tipranavir Open-Label Study

This expanded open-label study, sponsored by Boehringer Ingelheim, will provide access to tipranavir, an investigational nonpeptidic protease inhibitor (PI). This past autumn the company requested Food and Drug Administration approval to market the drug. This non-randomized trial will provide tipranavir to treatment-experienced individuals who are not benefiting from or unable to tolerate their current therapy and need a new PI to construct a viable regimen. All subjects will receive tipranavir plus ritonavir (Norvir); there is no placebo arm. Safety evaluations will be performed at regular intervals.

Prospective subjects must be at least 13 years old and must be unable to achieve virological suppression on their current antiretroviral regimen, with a maximum CD4 cell count of 100 cells/mm³ and/or a viral load of 10,000 copies/mL or greater. They must not have certain medical conditions and may not be taking certain other drugs. Women may not be pregnant or breast-feeding and must agree to use effective contraception.

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

TNX-355: New Entry Inhibitor

This double-blind Phase II study, sponsored by Tanox, will compare an investigational entry inhibitor, TNX-355, plus optimized background therapy (OBT) against OBT

alone in treatment-experienced individuals with resistant HIV. OBT will be selected based on subjects' past medication history and resistance tests, and may not include another entry or fusion inhibitor. Subjects will be randomly assigned to receive TNX-355, placebo, or alternating TNX-355 and placebo administered by intravenous infusion every week for eight weeks, then every two weeks until week 48. Participants who experience virological failure after week 16 will have the option of trying a new optimized background regimen plus open-label TNX-355; those who experience a second failure will be taken off the study.

Eligible subjects must be at least 18 years old. They must have an HIV viral load of at least 10,000 copies/mL, have been on stable highly active antiretroviral therapy (HAART) for at least four weeks at study entry, have a cumulative history of HAART use of at least six months, have used all three established classes of antiretroviral drugs (nucleoside reverse transcriptase inhibitors [NRTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs], and PIs), and have experienced virological failure with their current or a previous regimen. However, their HIV must be susceptible to at least one drug in the OBT regimen. Subjects may not have previously used HIV entry or fusion inhibitors. Other exclusion criteria include various medical conditions or abnormal lab tests and use of certain medications or vaccines. Women may not be pregnant or breast-feeding and participants must agree to use effective contraception.

The study aims to enroll 80 subjects at 15 sites including **Baltimore** (410-837-2050 ext. 1281), **Cincinnati** (513-584-8373), **Los Angeles** (323-869-5429), **Miami** (305-243-5621), **New Orleans** (504-895-0361), **Phoenix** (602-307-5330 ext. 2252), **San Juan** (787-723-5945 ext. 25), **Tampa** (813-870-4760 ext. 231), and **Washington, DC** (202-745-0201 ext. 20); www.clinicaltrials.gov/ct/gui/show/NCT00089700. (TNX-355.03)

UK-427,857: Two Studies Starting

In December two trials began to study the safety and antiviral efficacy of UK-427,857, an investigational HIV entry inhibitor. Both are sponsored by the drug's manufacturer, Pfizer. In lab studies UK-427,857—a reversible CCR5 coreceptor antagonist—was shown to be active against HIV, including virus resistant to existing classes of antiretroviral drugs. In early clinical trials UK-427,857 appeared safe in more than 400 subjects who took the drug for 28 days.

1) The first study will compare UK-427,857 vs efavirenz (Sustiva) in individuals starting anti-HIV therapy for the

first time. In this Phase I/II study subjects will be randomly assigned to receive 300 mg UK-427,857 once daily, 300 mg UK-427,857 twice daily, or efavirenz. Subjects in all three arms will also take AZT (zidovudine, Retrovir) and 3TC (lamivudine, Epivir). The treatment period will last 96 weeks, and may be extended depending on results at that point. Treatment involves regular clinic visits, some of which will include blood draws, electrocardiograms (heart rhythm monitoring), computerized tomography (CT, CAT) scans, and symptom questionnaires.

Eligible subjects must be at least 16 years old and have viral loads of at least 2,000 copies/mL. Exclusion criteria include various medical conditions or abnormal lab tests and current or prior use of certain medications (including efavirenz, AZT, or 3TC for more than 14 days). Women may not be pregnant or breast-feeding and participants must agree to use effective contraception.

This study will enroll more than 1,000 subjects at about 200 centers worldwide. For location and contact information, call Pfizer at 734-622-7600; www.clinicaltrials.gov/ct/show/NCT00098293. (A4001026)

2) The second study will compare UK-427,857 plus OBT vs OBT alone in treatment-experienced individuals. In this Phase II/III study subjects will receive an optimized antiretroviral regimen as determined by treatment history and resistance testing. In addition, they will be randomly assigned to receive 150 mg UK-427,857 once daily, 150 mg UK-427,857 twice daily, or placebo. The treatment period will last 48 weeks and may be extended for an additional year. Treatment involves regular clinic visits, some of which will include blood draws and electrocardiograms.

Eligible subjects must be at least 16 years old and have viral loads of at least 5,000 copies/mL. They must have been on stable HAART, or else no antiretroviral therapy, for at least four weeks. Subjects must have six months' cumulative experience with or documented resistance to three of the four existing classes of anti-HIV medications. Exclusion criteria include various medical conditions or abnormal lab tests and current or prior use of certain medications (including other experimental entry inhibitors). Women may not be pregnant or breast-feeding and participants must agree to use effective contraception.

This study aims to enroll 500 participants at 100 U.S. and Canadian centers, including **Dallas, Huntersville, NC,** and **New York City**. For more information, call 734-622-7600; www.clinicaltrials.gov/ct/show/NCT00098306. (A4001027)

SMART: Drug Conservation vs Viral Suppression

The SMART study, conducted by the CPCRA, is a large, simple trial comparing two HIV treatment strategies.

The study will attempt to determine whether participants at low risk of HIV disease progression can safely reduce their use of antiretroviral therapy, thus minimizing side effects, slowing the development of drug resistance, and conserving future treatment options. Participants randomly assigned to the viral suppression arm (the “GO” group) will continue, or start, treatment in an attempt to keep viral load as low as possible, regardless of CD4 cell count. Those assigned to the drug conservation arm (the “WAIT” group) will stop, or not start, anti-HIV therapy until their CD4 cell counts fall below 250 cells/mm³, at which point they will begin therapy and continue until their CD4 cell counts rise above 350 cells/mm³. Some 6,000 participants will be followed for an estimated 6–9 years, until about 900 primary events (disease progression or death) occur.

Participants must be at least 13 years old and have CD4 cell counts above 350 cells/mm³ within 45 days of study entry. Subjects may be using any available antiretroviral or immune-modulating drugs at study entry. They must be in reasonably good health and available to continue the study for at least six months. Women may not be pregnant or breast-feeding and participants must be willing to use effective contraception.

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

When to Start HAART in People with OIs

This study will attempt to determine the best time to start antiretroviral therapy in individuals presenting with opportunistic illnesses (OIs). Immediately starting HAART may be disadvantageous since anti-HIV drugs can lead to immune reconstitution syndrome (IRIS; see page 12) and can interact with drugs used to treat OIs. This trial will compare the benefits and drawbacks of starting antiretroviral therapy immediately vs waiting until after OI treatment is underway or completed. Participants will be randomly assigned to either begin antiretroviral therapy within two months of starting OI treatment, or to defer anti-HIV treatment until at least four weeks—but no more than 32 weeks—after beginning OI therapy. All subjects will receive Kaletra (lopinavir/ritonavir) plus d4T (stavudine, Zerit),

and may also receive a third and fourth anti-HIV drug at the discretion of study clinicians. The study will last 48 weeks and participants will have ten study visits, which will include blood tests, physical exams, and questionnaires.

Eligible participants must be at least 13 years old. They must have a confirmed or suspected acute OI, including *Pneumocystis carinii* pneumonia (PCP), bacterial pneumonia, cryptococcal meningitis, disseminated histoplasmosis, disseminated *Mycobacterium avium* complex (MAC), cytomegalovirus (CMV) retinitis or encephalitis, or toxoplasmic encephalitis. Participants may not have been on antiretroviral therapy within six months of study entry or for a total of six months at any time, and may not have been treated for their current OI for more than 14 days before study entry. Various medical conditions and recent use of certain medications are excluded. Women may not be pregnant or breast-feeding and subjects must be willing to use effective contraception.

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

Decreased Mental Function: Selegiline Patch

This double-blind Phase II study will examine whether the selegiline transdermal system (skin patch) is safe and effective in treating decreased mental function in people with HIV. Currently oral selegiline (Eldepryl) is approved for the treatment of Parkinson’s disease. Prospective subjects will undergo blood draws, lumbar punctures (spinal taps), and neuropsychological screening tests to determine cognitive function. Participants will be randomly assigned to receive patches with one of two doses of selegiline or placebo (inactive) patches, to be applied daily. Study visits will take place at weeks 4, 8, 12, 16, and 24. Visits at weeks 12 and 24 will include mental function tests and surveys; the week 24 visit will include another lumbar puncture. Participants who complete the first 24-week stage of the trial will have the option to take part in an additional 24-week, open-label stage.

Eligible participants must be at least 18 years old and have impaired mental functioning as indicated by prestudy screening tests. There are no CD4 cell count or viral load restrictions. Participants must have been on stable antiretroviral therapy for eight weeks before study entry, or off treatment for those eight weeks due to drug resistance or intolerance. Exclusion criteria include various medical

conditions (including AIDS-defining OIs and use of certain medications). Women may not be pregnant or breast-feeding.

This study will enroll 120 participants at about 20 sites, including **Baltimore** (410-614-4487), **Boston** (617-726-3819), **Chapel Hill** (919-843-8761), **Chicago** (312-695-5012 or 312-572-4545), **Dallas** (214-590-0414), **Denver** (303-372-5535), **Honolulu** (808-737-2751), **Los Angeles** (310-825-3594), **New York City** (212-420-4432 or 212-305-2665), **Philadelphia** (215-349-8092), **Rochester** (716-275-2740), **San Diego** (619-543-8080), **Seattle** (206-731-8877), and **St. Louis** (314-454-0058); www.clinicaltrials.gov/ct/show/NCT00013585. (ACTG A5090)

A substudy of ACTG A5090, known as ACTG A5114s, will use magnetic resonance spectroscopy (MRS; a type of noninvasive brain imaging) to compare the extent of cerebral injury and functionality in people with memory impairment before and after using selegiline patches. MRS will be performed at study entry and at week 24. Participants enrolled in ACTG A5090 are eligible for the substudy, which aims to enroll 90 subjects at about half the sites conducting the parent study, including those in **Baltimore, Los Angeles, New York City, Philadelphia, Rochester, San Diego, and Seattle**; www.clinicaltrials.gov/ct/show/NCT00027040. (ACTG A5114s)

Acetyl-L-Carnitine for NRTI-Associated Neuropathy

This study will attempt to determine whether acetyl-L-carnitine reduces pain, numbness, and tingling in the lower extremities of individuals with peripheral neuropathy associated with the use of NRTI drugs. Subjects will start with one acetyl-L-carnitine tablet twice daily, increasing to three tablets daily for the duration of the 24-week trial; this is an open-label study with no placebo arm. Participants will undergo regular clinic visits, some of which require fasting blood draws; they will also have two small skin biopsies at enrollment and at the end of the study.

Eligible subjects must be at least 13 years old and have evidence of predominantly sensory neuropathy. Their HIV viral loads must be below 10,000 copies/mL within 60 days of study entry. For at least eight weeks they must have been on stable antiretroviral regimens that include at least one dideoxynucleoside analog (NRTI) drug, such as ddI (didanosine, Videx) or d4T. Exclusion criteria include various medical conditions and use of certain drugs (including recently started pain medications or other investigational agents). Women may not be pregnant or breast-feeding and participants must agree to use effective contraception.

This study aims to enroll 36 participants at about ten sites, including **Baltimore** (410-614-2766), **Chicago** (312-572-4545), **Galveston** (409-747-0241), **New York City** (212-746-4393), **Sacramento** (214-590-0414), **Seattle** (206-731-8877), and **St. Louis** (314-454-0058); www.clinicaltrials.gov/ct/show/NCT00050271. (ACTG A5157)

Capsaicin for Neuropathy Pain

This trial will study the safety and efficacy of capsaicin (chili pepper extract) in treating HIV-associated neuropathy. Previous research has shown that capsaicin can help relieve neuropathic pain. In this double-blind Phase III study, sponsored by NeurogesX, subjects will be randomly assigned to use NGX-4010, a high-concentration capsaicin patch, or placebo for 12 weeks.

Eligible subjects must be at least 18 years old and have had HIV-associated neuropathy with moderate-to-severe pain in both feet for at least two months. Exclusion criteria include various medical conditions, history of substance abuse, and use of other topical pain medications. Women may not be pregnant.

This study will be conducted at about 20 sites, including **Annandale, VA** (703-560-4821), **New York City** (212-241-0784), and **Sarasota** (941-366-0776). Contact NeurogesX at 605-508-2116 or visit the web site for more locations; www.clinicaltrials.gov/ct/show/NCT00085761. (C112)

Peripheral Neuropathy Pain: Medical Marijuana

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

Prospective participants must be at least 18 years old and have painful HIV-related neuropathy. They must have been on a stable antiretroviral regimen, or else no anti-HIV treatment, for at least the previous eight weeks. They must have used marijuana on at least six occasions in the past, but not within 30 days of study entry. There are no CD4 cell count or viral load restrictions. Subjects may not have diabetes, uncontrolled high blood pressure, or heart or lung disease, and must not be using certain medications

(including corticosteroids). Current tobacco users are not eligible. Women may not be pregnant or breast-feeding.

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

Alpha-Lipoic Acid for Painful Neuropathy

This Phase I/II study will look at alpha-lipoic acid, a naturally occurring antioxidant, for the treatment of painful HIV-related neuropathy. Previous research has shown that the agent significantly improves pain associated with diabetic neuropathy. Subjects will be randomized to receive daily oral doses of alpha-lipoic acid (600 mg three times daily) or placebo for 24 weeks.

Eligible subjects must be at least 18 years old and have diagnosed distal sensory peripheral neuropathy with pain or paresthesias (unusual sensations), with or without numbness or weakness. They must have been on a stable antiretroviral regimen, or else no anti-HIV treatment, for 12 weeks before study entry. Exclusion criteria include significant cognitive impairment, other potential causes of neuropathy besides HIV, and use of certain medications. Women may not be pregnant and must agree to use effective contraception.

This study aims to enroll 60 participants at the University of North Carolina at **Chapel Hill** (919-966-8975); www.clinicaltrials.gov/ct/show/NCT00079807. (R21AT1775)

Fish Oil Plus Fenofibrate for High Triglycerides

This study will examine whether fish oil plus fenofibrate (Tricor) can help reduce elevated triglyceride levels in people taking antiretroviral therapy. In particular, the trial will study the effect of the combination in individuals who have not responded to either fish oil or fibrate drugs alone. In this open-label Phase II trial, participants will first be randomly assigned to receive either fish oil supplements containing omega-3 fatty acids or fenofibrate. Those who show a response at week 8 will stay on the single therapy through week 18; those who do not respond by week 10 will add the agent they did not initially receive, and will take both through week 18. Participants will be assigned to a lipid-lowering diet and exercise program that begins a month before study entry and continues for the duration of the trial. Subjects will have regular clinic visits that include fasting blood draws. There will also be a follow-up visit at week 22. Subjects will continue their existing HAART regimens throughout the study.

Eligible participants must be at least 18 years old and have been on HAART for at least three months before study entry, and on an unchanged regimen for at least four

weeks. They must have fasting LDL “bad” cholesterol levels of 160 mg/dL or less and fasting serum triglyceride levels of 400 mg/dL or greater within 28 days of study entry. Exclusion criteria include various medical conditions (including coronary heart disease, atherosclerosis, uncontrolled high blood pressure, and diabetes) and use of certain medications (including recent use of other lipid-lowering agents). Women may not be pregnant or breast-feeding and must agree to use effective contraception.

This study will enroll 100 participants at more than 30 sites, including **Atlanta** (404-616-6313), **Chapel Hill** (919-843-8761), **Chicago** (312-572-4545), **Cleveland** (216-778-5489), **Dallas** (214-590-0414), **Honolulu** (808-737-2751), **Los Angeles** (310-206-8029), **Miami** (305-243-3838), **Minneapolis** (612-625-1462), **Nashville** (615-467-0154 ext. 108), **New York City** (212-420-4432), **Omaha** (402-559-8163), **Rochester** (585-275-2740), **San Francisco** (415-514-0550 ext. 354), **San Juan** (787-759-9595), **Seattle** (206-731-8877), and **St. Louis** (314-454-0058); www.clinicaltrials.gov/ct/show/NCT00076518. (ACTG A5186)

Bone Mineral Density: Alendronate, Calcium, and Vitamin D

This study will examine the effects of alendronate (Fosamax), calcium, and vitamin D on bone mineral density in people with HIV. Research has shown that HIV positive individuals appear to be at greater risk for bone loss (osteopenia and osteoporosis) due to antiretroviral therapy or HIV itself. In this Phase II safety and efficacy study, participants will be randomly assigned to receive either alendronate or placebo for 48 weeks; all subjects will receive calcium and vitamin D supplements. Participants will have regular clinic visits, which will include fasting blood draws and dual energy x-ray absorptiometry (DEXA) scans to evaluate bone density.

Eligible subjects must be at least 25 years old and have decreased bone mineral density as shown by a lumbar spine DEXA scan within 90 days of study entry. Subjects must have been on stable antiretroviral therapy for at least 12 weeks before enrollment, and must have CD4 cell counts of at least 100 cells/mm³ and HIV viral loads of 5,000 copies/mL or less. They must also have a serum calcium level between 8 and 11 mg/dL. Men may not have untreated hypogonadism (low testosterone), and women on estrogen replacement therapy and individuals on steroids must have been on stable regimens for at least 24 weeks. Exclusion criteria include various medical conditions (including esophagitis and recent spinal fractures) and use of certain medications and supplements (including glucocorticoids, calcium, vitamin D, or high doses of vitamin A). Women may not be pregnant or breast-feeding and must agree to use effective contraception.

This study is expected to enroll 80 participants at about 25 sites, including **Birmingham** (205-975-9128), **Chapel Hill** (919-843-8761), **Chicago** (312-695-5012), **Cleveland** (216-778-5489), **Galveston** (409-747-0241), **Indianapolis** (317-274-8456), **Los Angeles** (310-206-8029), **Minneapolis** (612-625-1462), **Nashville** (615-467-0154 ext. 108), **New York City** (212-263-6565), **Omaha** (402-559-8163), **Philadelphia** (215-349-8092), **Rochester** (585-275-2740), **San Francisco** (415-514-0550 ext. 354), **Seattle** (206-731-8877), and **Washington, DC** (202-687-7387); www.clinicaltrials.gov/ct/show/NCT00061256. (ACTG A5163)

Therapeutic Vaccine Plus Treatment Interruption

This study will examine the effectiveness of an HIV therapeutic vaccine followed by treatment interruption. It is intended to test the theory that vaccination may generate a long-term immune response against HIV if given while viral replication is controlled by antiretroviral therapy. While still taking their antiretroviral medications, participants will be randomly assigned to receive either the MRK Ad5 HIV-1 Gag vaccine (which uses a replication-defective adenovirus vector) or placebo injections on day 1 of the study and at weeks 4 and 26. Three months after the final injection, they will stop taking their anti-HIV drugs, and changes in viral load and CD4 cell count will be observed for four months. After this period participants will have the option of restarting anti-HIV therapy or continuing without medication; they will be followed every two months for eight more months. Further follow-up by phone will continue biannually for an additional 3.5 years.

Eligible participants must be at least 18 years old, HIV positive, and have been on stable antiretroviral therapy for at least four weeks. They must have viral loads below 50 copies/mL at study entry and documented viral suppression (below 500 copies/mL) for the two preceding years, but must have had at least one documented viral load measurement of 1,000 copies/mL or more within the two years before starting antiretroviral treatment. CD4 cell counts must be at least 500 cells/mm³. Participants may not be coinfecting with hepatitis B or C and may not have a history of OIs or various conditions (including heart, liver, or kidney disease). They may not be taking certain drugs and may not have received certain other vaccines. Women may not be pregnant or breast-feeding and participants must agree to use effective contraception.

The study is expected to enroll 120 participants at about 30 sites, including **Baltimore** (410-706-2785), **Boston** (617-724-0072), **Chapel Hill** (919-843-8761), **Cleveland** (216-778-5489), **Dallas** (214-590-0414), **Denver** (303-372-5535), **Honolulu** (808-737-2751), **Los Angeles** (310-825-1301),

Miami (305-243-3838), **Minneapolis** (612-625-1462), **New York City** (212-420-4432 or 212-746-7198), **San Francisco** (415-514-0550 ext. 354), **San Juan** (787-759-9595), **Seattle** (206-731-8877), and **St. Louis** (314-454-0058); www.clinicaltrials.gov/ct/show/NCT00080106. (ACTG A5197)

Other Therapeutic Vaccine Strategies

Other smaller therapeutic vaccine trials are recruiting participants at single sites.

1) In one nonrandomized, open-label study, ten subjects will receive injections of an HIV-antigen-bearing dendritic cell vaccine. They will then stop their antiretroviral medications, and CD4 cell count and viral load will be monitored for 12 weeks. Eligible participants must be 18–60 years old and may be either HIV positive or negative. They must have baseline CD4 cell counts of at least 400 cells/mm³ and, if HIV positive, viral loads below 50 copies/mL; positive subjects also must have started antiretroviral therapy within 120 days of infection. Participants must also have the HLA-A*0201 (HLA A2.1) blood type. There are various exclusion criteria related to medical conditions and use of other medications. Women may not be pregnant or breast-feeding.

This trial is being conducted in **Boston** (617-724-9690); www.clinicaltrials.gov/ct/show/NCT00058734. (R01 AI44628)

2) Another study is looking at the immune-enhancing properties of a vaccine made from participants' own (autologous) dendritic cells in subjects who remain on HAART throughout the trial. Two doses of dendritic cells will be tested, and subjects will be followed for 48 weeks. Participants must have at least 400 CD4 cells/mm³, viral loads below 400 copies/mL, and the HLA-A*0201 blood type. There are various exclusion criteria related to medical conditions, use of other medications and vaccines, and pregnancy.

This study will recruit 18 participants in **Pittsburgh** (412-647-8125 or 888-396-7838); www.clinicaltrials.gov/ct/show/NCT00056758. (P01 AI43664-04)

3) A third study is looking at whether a recombinant HIV-specific canarypox vaccine known as ALVAC vCP1452, with or without low-dose interleukin 2 (IL-2, Aldesleukin), can control HIV viral load after antiretroviral therapy is stopped. Participants will be randomly assigned to receive either the active vaccine alone, placebo alone, IL-2 plus active vaccine, or IL-2 plus placebo. The vaccine, placebo, and IL-2 all require multiple injections. In step 2 of the study subjects in all arms will stop HAART for at least 12

weeks, and viral load will be monitored. Participants whose viral loads stay below 30,000 copies/mL will remain off HAART and continue weekly viral load monitoring. Those whose viral loads increase to more than 30,000 copies/mL or whose CD4 cell counts fall below 200 cells/mm³ will restart antiretroviral therapy. Eligible participants must be at least 19 years old and have been on their current HAART regimen for more than six consecutive months. They must have CD4 cell counts of at least 400 cells/mm³ within 30 days of study entry and at least 200 cells/mm³ during the past year. Viral load must be below 50 copies/mL within 30 days of study entry. There are various exclusion criteria related to medical conditions and use of other medications. Women may not be pregnant or breast-feeding.

This study seeks to enroll 92 participants in **New York City** (212-746-4361); www.clinicaltrials.gov/ct/show/NCT00013663. (B012; 0900-397)

Project T: Tenofovir to Prevent HIV Infection

This study, coordinated by the Centers for Disease Control and Prevention (CDC), is part of a larger international research program to determine whether the nucleotide reverse transcriptase inhibitor tenofovir DF (Viread) can help prevent HIV infection. The drug has performed well in animal prophylaxis studies and appears to have fewer side effects than other antiretroviral medications. *The U.S. phase of the study will focus on the clinical and behavioral safety of the drug, not its effectiveness.* In particular, researchers will attempt to determine whether using a potentially preventive drug will lead to an increase in risky sexual behavior. Participants in arm A will receive either 300 mg daily oral tenofovir or placebo; those in arm B will wait nine months before starting therapy. Because it is not yet known whether tenofovir can help prevent HIV infection—and because some subjects will be taking placebo—participants should continue to practice safer sex, and will receive risk-reduction counseling and free condoms during the study. Should any participants become infected, the local research group will facilitate referrals for HIV care and treatment.

Eligible participants must be sexually active, HIV negative men who have sex with men between the ages of 18 and 60. The study is expected to last two years.

The U.S. arm of the study will enroll 200 gay and bisexual men at each of two sites, **Atlanta** (404-876-2317) and **San Francisco** (415-554-8888; www.sf aidsresearch.org).

ACE: Herpes Suppression to Prevent HIV Infection

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

Eligible participants must be sexually active, HIV negative gay or bisexual men at least 18 years old with confirmed HSV-2 infection.

The study will enroll 315 participants in **New York City** (212-388-0008; www.projectachieve.org), **San Francisco** (415-437-4782; www.sf aidsresearch.org), **Seattle** (206-520-3800 or 800-464-9063), and **Lima, Peru**.

A similar study of heterosexual women is being conducted in **South Africa, Zambia, and Zimbabwe**; www.hptn.org/research_studies/hptn039.asp. (HPTN 309)



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