Bulletin of Experimental Treatments for AIDS

BETA

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31

Non-Hodgkin's Lymphoma
18

Paying for Life
24

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notice

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editor's note

As in each edition of BETA, *the Summer 2003 issue includes a selected listing of enrolling clinical trials (page 44). I urge readers not to pass over this section. Clinical research can propel us toward better therapies (page 13) and an eventual cure, but without study participants there will be little forward movement. Progress depends on large numbers of volunteers of every background and body type. This is especially true of women with HIV, who often do not receive sex-specific care in part because most treatment research has been done in men (page 40).*

In this issue readers will find a feature article on the variety of tests that are done to monitor the health of people with HIV (page 31), as well as a look at non-Hodgkin's lymphoma, an AIDS-defining cancer that can be difficult to treat (page 18). Bob Huff demystifies the cost of anti-HIV medication in "Paying for Life" (page 24). And, as always, our News Briefs column (page 4) highlights recent developments related to HIV/AIDS at scientific conferences and elsewhere.

Nicholas

IN THEIR OWN WORDS: SAC SPEAKS

BETA *asked members of its San Francisco-based Scientific Advisory Committee (SAC) the following question:*

What health advice would you give to readers?

George Beatty, MD, MPH

Everyone is worried about cardiovascular disease risk associated with anti-HIV drugs. The drugs may contribute a certain amount to heart disease, but the risk reduction would be huge if people quit smoking and paid attention to other classic risk factors. I'd also encourage people with HIV not to tweak on speed (methamphetamine).

Cristina Gruta, PharmD

Anti-HIV medications can interact with other medications, including over-the-counter drugs, herbs, and recreational agents. Always let your provider know everything you're taking so that any untoward effects of drug interactions can be minimized.

Greg Pauxtis, MD

Keep an eye on triglycerides, and make sure both cholesterol and triglyceride levels are under control. I know men in their early fifties with angina and other heart disease because their triglyceride levels are being ignored. I would also encourage men not to abuse testosterone therapy, which can lead to problems like liver function abnormalities and nerve displacement in the arms.

Eric Goosby, MD

Everyone—especially in minority group populations—should keep in mind that the relationship you have with a knowledgeable health-care provider can have a profound impact on your health. It's not just a question of having a provider, but of having one you trust and are comfortable with. If the relationship with your provider isn't satisfactory, change to someone else. Also, HIV positive people shouldn't have a false sense of security if their viral load is undetectable—they are still able to transmit HIV.

Lisa Capaldini, MD

Make sure there is a healthy source of day-to-day happiness in your life: a dog, a hobby, a partner, a spiritual practice. Also, before every medical visit make a list addressing the following questions:

- How am I doing in general?
- Am I having any side effects from my meds?
- How is my medication adherence?

Let your clinician know if there are problems in any of these areas.

NEWS BRIEFS

Liz Highleyman

For the latest updated HIV treatment guidelines for adults, adolescents, children, and pregnant women; postexposure prophylaxis (PEP) guidelines for occupational and nonoccupational exposure; and opportunistic illness (OI) prevention guidelines, visit www.aidsinfo.nih.gov.

10TH RETROVIRUS CONFERENCE

The 10th Conference on Retroviruses and Opportunistic Infections, the major U.S. scientific meeting on HIV, took place February 10–14, 2003, in Boston. The conference drew nearly 4,000 participants and more than 800 abstracts were presented. The Retrovirus conference covered the full gamut of issues related to HIV, from global treatment access to managing opportunistic illnesses (OIs). But the primary themes were advances in antiretroviral therapy, novel treatment strategies, and treatment-related problems (including resistance and metabolic complications).

When to Start and What to Use

Despite the potential drawbacks of treatment, researchers and physicians agree that the benefits of starting combination anti-HIV therapy before CD4 cell counts fall below 200 cells/mm^3 outweigh the disadvantages. Jonathan Sterne, PhD, and colleagues from the ART Cohort Collaboration (abstract 181) reported that CD4 cell counts and viral loads six months after starting therapy predict the development of AIDS-related illnesses and death better than baseline levels. E. Ferrer and colleagues from Barcelona (abstract 910) presented evidence suggesting that it may be better to start therapy before CD4 cell counts fall below 350 cells/mm^3 (the recommended level in the current U.S. HIV treatment guidelines), but the exact best time to start treatment remains an open question.

The same is true for which regimen to start with. With many new anti-HIV drugs available, there is much more flexibility than in the past, including several once-daily options. Frank van Leth, MD, from the International Therapy Evaluation Center in Amsterdam and colleagues (abstract 176) presented the long-awaited first results from the multinational "2NN" study comparing the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz (Sustiva) and nevirapine (Viramune)—both alone and combined—along with d4T (stavudine, Zerit) and 3TC (lamivudine, Epivir). Overall, efavirenz and once- or twice-daily nevirapine performed comparably well, although efavirenz was slightly (about 5%) more likely to suppress HIV—not a statistically significant difference—and appeared to work better in people with high viral loads. Nevirapine was more likely to cause serious side effects including liver toxicity and severe rash (one death due to each), while efavirenz caused more transient central nervous symptoms including bizarre dreams and sleep problems. Importantly, the study failed to demonstrate that using two NNRTIs provided additional benefit compared with just one, although considerably more people who used both NNRTIs together dropped out of the study due to side effects.

On the nucleoside reverse transcriptase inhibitor (NRTI) front, Schlomo Staszewski, MD, of Goethe-Universität in Frankfurt and colleagues (abstract 564b) reported that while tenofovir DF (TDF, Viread) and d4T appear to suppress HIV equally well, d4T is more likely to be associated with elevated blood fat levels and lipoatrophy (fat loss). Brian Kearney and colleagues from Gilead Sciences (abstract 533) presented results of a study of coadministration of tenofovir and once-daily ddI (didanosine, Videx). Because tenofovir increases ddI concentrations, ddI can be taken at a lower dose (250 mg once daily) with a light meal when used with tenofovir. While several presentations touted the benefits of tenofovir, there have been some disturbing reports of kidney toxicity associated with the drug (see news item below).

Treatment Delay and Interruption

Structured treatment interruption (STI) remains a controversial issue, and the conflicting results presented at the Retrovirus conference did little the resolve the debate. Jody Lawrence, MD, from the University of California at San Francisco (UCSF) (abstract 67) reported results from CPCRA 064 comparing immediate use of a new antiretroviral regimen against a four-month interruption prior to starting new therapy. Participants were 270 heavily treated individuals with advanced HIV disease who were experiencing treatment failure. After about a year of follow-up, 22 participants experienced disease progression or death in the deferred therapy arm, compared with 12 in the immediate therapy arm. The deferred group also had poorer CD4 cell responses when they restarted therapy. Because the delayed therapy arm was doing worse, a Data and Safety Monitoring Board halted new enrollments. The researchers recommended that people with multidrug-resistant HIV should not interrupt therapy before switching to a new regimen.

In contrast, Christine Katlama, MD, from Hôpital Pitié-Salpêtrière in Paris and colleagues (abstract 68) studied 68 heavily treated participants with advanced disease in the GIGHAART study who were also experiencing treatment failure. Compared with the CPCRA study, subjects in this trial had lower baseline CD4 cell counts and HIV that was resistant to more drugs. Participants were randomized to start treatment with a six- to eight-drug regimen immediately or after a delay of eight weeks. Unlike in the CPCRA study, viral load reductions were better in the participants who deferred therapy (38% undetectable vs 15% undetectable in the immediate arm) and CD4 cell increases were greater (69 cells/mm^3 in the deferred group vs 7 cells/mm^3 in the immediate arm).

Steven Deeks, MD, of UCSF (abstract 640) presented data on treatment-experienced people who stopped taking an entire class of drugs. Dr. Deeks had previously shown that when drugs are interrupted, wild-type (nonmutated) HIV usually overcomes less fit drug-resistant strains, which do not replicate as well; when people restart the same treatment, the drug-resistant HIV tends to come back. In Dr. Deeks's latest study, 15 people stopped taking all protease inhibitors (PIs), while five discontinued all NRTIs. Those who stopped PIs and continued NRTIs maintained stable viral loads and CD4 cell counts, while their blood fat levels decreased. Those who stopped NRTIs but continued PIs, however, experienced dramatic and rapid viral load increases (this arm of the study was halted). These intriguing results suggest that staying on "failing" NRTIs can still provide virological benefit. According to Dr. Deeks, such partial treatment interruptions may serve as a "bridge therapy" until better anti-HIV drugs become available.

Mark Dybul, MD, of the National Institute of Allergy and Infectious Diseases (NIAID) (abstract 68LB) reported on long-cycle treatment interruptions. In one study, 52 participants with baseline CD4 cell counts above 300 cells/mm^3 and viral loads below 50 copies/mL were randomized to receive continuous therapy or treatment on an eight-weeks-on/four-weeks-off schedule. Study enrollment was halted due to the emergence of drug resistance in those starting and stopping therapy, and there was no significant reduction in blood fat levels in the cycling arm at 48 weeks. Stephano Vella, MD, of the Istituto Superiore di Sanità in Rome and colleagues (abstract 66) compared continuous and intermittent therapy (cycles of three months on followed by one or two months off) in a group of 273 participants. After the first, second, and third interruptions, 88.9%, 96.8%, and 100%, respectively, achieved viral loads below 400 copies/mL (vs 100% in the continuous therapy arm). However, after six months those in the intermittent arm were more likely to develop resistance.

Other researchers presented results from studies of open-ended treatment interruptions guided by CD4 cell count rather than continued for a set period of time. Jintanat Ananworanich, MD, from the Thai Red Cross AIDS Research Center in Bangkok and colleagues (abstract 64) compared continuous treatment, treatment interruptions that lasted as long as CD4 cell counts remained above a predetermined threshold, and one-week-on/one-week-off treatment cycles. After one year, those using the CD4 cell count-guided strategy took drugs for a shorter total time (about one-third of the year) and had better viral suppression. Luis Ruiz, MD, and colleagues from Barcelona (abstract 65) also looked at CD4 cell count-guided treatment interruptions. Participants began with baseline CD4 cell counts above 500 cells/mm^3, nadir (lowest ever) CD4 cell counts above 100 cells/mm^3, and viral loads below 80 copies/mL. During one year of observation, 57% restarted therapy because their CD4 cell counts fell below 350 cells/mm^3 and/or their viral loads increased to more than 100,000 copies/mL, while 43% were able to stay off treatment with no apparent disease progression.

In summary, while timed treatment interruptions appear to yield little benefit, open-ended interruptions based on CD4 cell counts—as well as the new partial treatment interruption strategy—show some promise, but require further study.

Metabolic Complications

Numerous presentations at the Retrovirus conference dealt with metabolic manifestations related to anti-HIV therapy, including lipodystrophy, elevated blood fat levels, diabetes, reduced bone mass, and the potential for increased cardiovascular disease risk (see "HAART and the Heart" news item below). The first results from the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study were presented in three posters (abstracts 732, 733, and 734). FRAM is comparing 1,200 HIV positive men from multiple U.S. sites with 300 HIV negative participants enrolled in the CARDIA heart health study. Based on results to date, lipoatrophy (fat loss in the limbs, buttocks, and face) is the most common manifestation of fat abnormalities in men with HIV, and is not associated with abdominal fat gain. In this study abdominal fat accumulation and "buffalo hump" (fat accumulation at the back of the neck) occurred slightly more often in the HIV negative men, although the HIV positive men had larger "humps." Notably, FRAM is a cross-sectional study that looks at subjects at a single point in time; longitudinal studies that follow patients over time should provide more useful information.

In the area of elevated blood fat and glucose (sugar) levels, several presentations (including the "2NN" study described above and studies of fos-amprenavir described below) looked at how various drugs differentially affect lipid levels and insulin resistance. Research continues to implicate d4T as a major culprit in mitochondrial toxicity (damage to the energy-producing components of cells) and lipoatrophy; several studies have shown that switching from d4T to another NRTI can alleviate peripheral fat loss (in the extremities) (abstracts 133, 727, 728, and 729). Mark Boyd,

MD, and colleagues from the HIV Netherlands/Australia/Thailand Research Collaboration (abstract 738) found that subjects who stopped all NRTIs in favor of an indinavir (Crixivan)/ritonavir (Norvir)/efavirenz regimen gained back lost peripheral fat, but also gained visceral (intra-abdominal) fat and decreased lean body mass (muscle tissue).

In the general population, postmenopausal women are more susceptible to reduced bone mineral density (osteopenia and osteoporosis) compared with men of the same age, but the condition has not been well studied in women with HIV. Two studies presented at the conference did not find lower bone mass to be a major problem in HIV positive women. In one study (abstract 102), bone loss was minimal—0.5% per year—among women with high CD4 cell counts, and no association was seen with anti-HIV therapy. In the other (abstract 103), the rate of osteopenia or osteoporosis in HIV positive women (30%) was not significantly different from that of HIV negative controls (24%). Notably, in both studies a majority of the women were African American, and black women appear to be less susceptible to bone loss than white or Asian women; many of the women were overweight, also a protective factor. In terms of treatment, Pablo Tebas, MD, and colleagues from Washington University in St. Louis (abstract 134) reported that in a small study of 31 participants (mostly men), alendronate (Fosamax) plus calcium and vitamin D improved spinal bone density in HIV positive people with osteopenia or osteoporosis.

As has become clear over the past several years, metabolic abnormalities in people with HIV are a complex phenomenon. The conflicting, and in some cases unexpected, results presented at the Retrovirus conference shed more light on the issue, but do not yet provide definitive answers.

New Drugs

Researchers at the conference presented studies of many new drug candidates that may provide better options both for people just starting treatment and those who have exhausted current therapies. Although many of these experimental candidates will not be available for several years, researchers and people with HIV are encouraged by the fact that the drug pipeline is fuller than it has been in years.

Several new PIs are under study. GlaxoSmithKline's fos-amprenavir, or 908, is a more potent prodrug of amprenavir (Agenerase) that can be taken as two pills once or twice daily and does not require boosting with ritonavir; it is expected to be approved within the year. In the NEAT trial, fos-amprenavir suppressed HIV better than nelfinavir (Viracept) in treatment-naive individuals, and in the CONTEXT trial it worked almost as well as lopinavir (Kaletra) in treatment-experienced people. Bristol-Myers Squibb's atazanavir (Reyataz) provides good viral suppression in treatment-naive individuals and appears less likely to cause elevated blood fat levels or insulin resistance. (Atazanavir was recently approved; see news item below.) Boehringer Ingelheim's tipranavir, now in Phase III trials, is being touted as an option for treatment-experienced individuals. The first nonpeptide PI, it shows activity against HIV that is resistant to many other PIs. Due to its poor bioavailability, tipranavir requires boosting with ritonavir to achieve a reasonable daily pill burden. Other PIs further back in the pipeline include Tibotec's TMC114 and TMC125, and Roche's RO0334649.

Other new drugs in existing classes include emtricitabine (FTC, Emtriva), an NRTI related to 3TC that can be taken once daily; it also works against hepatitis B. While seen by many as a "me too" drug—one that does not offer a major advance—some believe its advantage lies in the creation of a once-daily emtricitabine/tenofovir combination pill. [Ed. note: FTC was approved in early July.] In Phase II studies, Pharmasset's racivir (another NRTI) appears to have a delayed effect that may allow less than once-daily dosing. GW4751 and related drugs are a new type of NNRTI that works against HIV with the K103N NNRTI-resistance mutation.

New drug classes also garnered considerable attention at the conference. Based on very preliminary data, Roche/Trimeris' second-generation fusion inhibitor, T-1249, appears to be active against HIV that has developed resistance to the recently approved T-20 (see news item below). Another type of entry inhibitor, CCR5 blockers, interfere with the attachment of HIV to host cell coreceptors; candidates in the pipeline include Pfizer's UK-427,857 (Phase I/II), Ono's AK602 (preclinical studies), and Takeda's TAK-220. Because chemokines such as CCR5 have other functions in the body, CCR5 inhibitors potentially could have serious side effects. Researchers from the Rega Institute in Belgium presented data on a new class of integrase inhibitors (including V-156) that prevent HIV from splicing its genetic material into the host cell's DNA. Panacos' PA-457, a betulinic acid derivative, inhibits assembly and budding of new HIV virions (virus particles).

Two other approaches that received a great deal of attention at the conference were monoclonal antibodies and RNA interference (RNAi). Tanox's monoclonal antibody, TNX-355, inhibits HIV attachment by binding to host cell CD4 receptors. Small interfering RNA (siRNA) are bits of genetic material that can "silence" the expression of genes and the production of certain proteins. Although an interesting concept, it is unclear whether RNAi will provide

FOR CONFERENCE PROGRAM AND ABSTRACTS

www.retroconference.org/2003

FOR DETAILED CONFERENCE COVERAGE

www.thebody.com/confs/retro2003/retro2003.html

www.hivandhepatitis.com/2003icr/10thretro/main.html

www.natap.org/2003/Retro/ndxRetro.htm

clinical benefit. For more information on several of the new experimental therapies presented at the Retrovirus conference, see "TMC114 and Other Investigational Drugs for Salvage Therapy" on page 13.

ATAZANAVIR APPROVED

On June 20 the U.S. Food and Drug Administration (FDA) approved Bristol-Myers Squibb's new PI, atazanavir (Reyataz). The drug provides good viral suppression in treatment-naive individuals (comparable to that of lopinavir, efavirenz, or nelfinavir) and appears less likely to cause elevated blood fat levels, although it may still contribute to lipodystrophy. Atazanavir is expected to be approved as a once-daily option for first-time therapy, since HIV that develops resistance to the new drug may still be sensitive—perhaps even hypersensitive—to other PIs. When used in treatment-experienced people, atazanavir may need to be boosted with ritonavir to achieve optimal potency. Safety results to date appear positive, although some questions remain about atazanavir's possible liver toxicity (the drug causes elevated bilirubin levels and jaundice in some people, similar to indinavir) and cardiac toxicity (it is associated with heart rhythm abnormalities).

T-20 (FUZEON) APPROVED

On March 13 the FDA approved T-20 (enfuvirtide, Fuzeon), the long-awaited first entry inhibitor drug. T-20 works by preventing HIV from fusing with cell membranes and entering host cells. It was developed by Trimeris, and is being produced and marketed in partnership with Roche.

T-20 was approved as salvage therapy for treatment-experienced individuals who have exhausted other anti-HIV therapy options. Two Phase III studies—TORO 1 and TORO 2—showed that T-20 added to an optimized antiretroviral regimen reduced viral load and increased CD4 cell counts in people with multidrug-resistant HIV. At 48 weeks, 30% of participants taking T-20 achieved viral loads below 400 copies/mL, compared with 12% of those on an optimized regimen without T-20. These results were presented at the Retrovirus conference and published in the May 29, 2003 issue of the *New England Journal of Medicine* (*NEJM*). T-20 does allow the development of drug resistance in some people. T-1249, an experimental entry inhibitor candidate from the same manufacturer, may work against T-20–resistant HIV (see "TMC114 and Other Investigational Drugs for Salvage Therapy" on page 13).

Unlike other approved anti-HIV drugs, T-20 powder must be mixed with sterile water and injected under the skin twice daily. People using T-20 are likely to experience reactions at the injection site, including pain, swelling, and hard nodules. People taking T-20 should immediately report to their health-care providers any symptoms that may indicate pneumonia (cough, fever, or difficulty breathing) or a hypersensitivity reaction (rash, fever, chills, vomiting, shortness of breath, or low blood pressure).

T-20 is difficult to produce—requiring more than 100 manufacturing steps—and comes with a correspondingly high price tag. At about $50 per day or $20,000 per year, it is more than twice as expensive as the next most costly anti-HIV drug. Advocates fear that the high price will make it difficult for Medicaid to pay for T-20, and impossible for many AIDS Drug Assistance Programs (ADAPs) to include the drug in their formularies. Several ADAP officials have met with Roche to request deep discounts for the drug. (For more on T-20 and drug pricing issues, see "Paying for Life" on page 24.)

Meanwhile, Roche and Trimeris have established a Reimbursement Assistance Program to help guide patients through the third-party reimbursement process, and a Patient Assistance Program to provide the drug at reduced cost. In addition, the companies announced a Progressive Distribution Program (PDP) to manage the initially limited supply of the drug and help ensure uninterrupted access. T-20 will be available only through the PDP, and will be allocated on a first-come, first-served basis. (This will likely be a disadvantage to those who must wait for a decision from their state ADAPs about whether the drug will be covered.) The companies expect to be able to provide T-20 to 12,000–15,000 people worldwide by the end of 2003—about 10,000 of these in the U.S.—and 32,000 people in 2004.

Physicians may enroll patients by phone, fax, or mail. Enrollment forms are available at www.fuzeon.com. Once enrollment is approved, a 30-day supply of the drug will be shipped to the patient's home, the physician's office, or a local Chronimed/StatScript pharmacy. For more information, including injection instructions, call 866-694-6670 or visit the web site.

NEW DRUG FORMULATIONS

In April the FDA approved a new formulation of Agouron/Pfizer's PI nelfinavir (Viracept). The new 625 mg tablet allows a dosage of two pills twice daily, compared with five of the previous 250 mg tablets twice daily. Any reduction in pill burden is likely to have a positive effect on adherence.

Also, this past December the FDA approved a new extended-release formulation of d4T (stavudine, Zerit) that can be taken once daily. Studies have shown that the new formulation—marketed as Zerit XR—is as effective as the older twice-daily version, yet maintains adequate drug concentrations in the blood for a longer period and can suppress HIV replication for 24 hours after dosing. (Note: the original twice-daily formulation should not be taken once per day as a doubled dose of two capsules.) With once-daily drugs, adherence is especially important since more time elapses between doses, potentially allowing resistance to develop if a dose is missed.

SOLO TRIZIVIR STUDY ARM HALTED

In March NIAID halted one arm of AIDS Clinical Trials Group (ACTG) study 5095, looking at protease-sparing

anti-HIV regimens, after early results showed that Trizivir (a combination pill containing AZT, 3TC, and abacavir) used alone was less effective than two combination regimens. After an average of 32 weeks, 79% of the treatment-naive participants taking only Trizivir achieved viral loads below 200 copies/mL, compared with 90% of those taking either Trizivir plus efavirenz or Combivir (AZT/3TC) plus efavirenz. Treatment failure occurred earlier and more often in the Trizivir-only arm regardless of initial viral load. NIAID issued a letter to health-care providers informing them of the decision to alter the trial. Results to date suggest that a single-class regimen containing only NRTIs may not be sufficiently potent to control HIV over the long term. In related news, the British HIV Association released new draft treatment guidelines at its April conference that recommend avoiding Trizivir alone as a first-line therapy due to its suboptimal efficacy.

TENOFOVIR KIDNEY TOXICITY

Just over a year after the approval of tenofovir DF (Viread) in October 2001, the first reports of severe kidney toxicity (nephrotoxicity) associated with the drug began to appear in medical journals. Experts have been on the alert for this side effect since a similar drug—adefovir (Preveon)—failed to gain FDA approval as an anti-HIV treatment due to nephrotoxicity. Another related drug—cidofovir (Vistide), used to treat cytomegalovirus (CMV) retinitis—is also known to cause kidney damage. Although high doses of tenofovir caused kidney failure in animal studies, serious kidney toxicity was rare in human clinical trials of the drug.

In the December 2002 issue of the *American Journal of Kidney Diseases,* David Verhelst from Hôpital Tenon in Paris and colleagues reported on a 45-year-old woman who developed acute renal (kidney) failure and Fanconi syndrome (disruption of the kidneys' normal activity) five months after adding tenofovir to her anti-HIV regimen. In the April 11 edition of *AIDS,* Caroline Créput and colleagues from France reported a case of kidney damage in a 60-year-old man treated with tenofovir. And the April 15, 2003 issue of *Clinical Infectious Diseases* contained two articles on tenofovir-related nephrotoxicity. The first, by Alexandre Karras and colleagues from Hôpital Saint-Louis in Paris, concerned three cases of kidney toxicity, including renal failure and proximal tubular dysfunction. The second article, by Melissa Murphy, MD, and colleagues from Oregon Health and Science University in Portland, concerned a 49-year-old man with stable pre-existing impaired kidney function who died due to kidney failure and lactic acidosis several weeks after adding tenofovir to his regimen (which also included ddI).

Finally, in April researchers from Vancouver reported at the 12th Annual Canadian Conference on HIV/AIDS Research the results of a study of kidney toxicity in patients attending local HIV clinics, 322 of whom received tenofovir and 430 of whom received abacavir (Ziagen). In this study, the researchers reported kidney dysfunction if a person had a creatinine level 1.5 times normal (as opposed to the severe grade 3 or 4 creatinine elevations counted in tenofovir clinical trials). The researchers found that the tenofovir users were about three times more likely to develop elevated creatinine levels compared with those taking abacavir. Overall, about 7% of the participants receiving tenofovir in this study showed some degree of kidney dysfunction, and six stopped the drug due to nephrotoxicity.

These data indicate that it is important for people taking tenofovir to have their kidney function monitored regularly, including measurements of serum creatinine, electrolytes, and sugar and protein in the urine. Symptoms of kidney dysfunction—including unusual thirst, frequent urination, edema (swelling), fatigue, and muscle weakness—should be reported immediately to a health-care provider.

CONTROVERSIAL AIDSVAX VACCINE RESULTS

On February 24 researchers from VaxGen announced initial results from a three-year randomized, controlled Phase III trial of its recombinant vaccine candidate, AIDSVAX. The vaccine is designed to stimulate the production of antibodies that attach to HIV's gp120 envelope protein, thus preventing the virus from binding to and entering cells. The vaccine did not significantly decrease the risk of HIV infection overall, but data suggest that it may be effective in certain racial groups.

The analysis included 5,009 high-risk volunteers in the U.S., Canada, and the Netherlands who received at least three doses of either AIDSVAX or a placebo; 4,185 were white, 326 were Hispanic, 314 were black, and 184 were Asian, mixed race, or other. Overall, the infection rate was 3.8% lower in vaccine recipients than in those who received the placebo—not a statistically significant difference. However, the rate was 67% lower among all non-white/non-Hispanic vaccine recipients, and 78% lower among black vaccine recipients; non-whites seemed to produce more antibodies in response to the vaccine. Statistical analysis showed that in the non-white volunteers, the vaccine appeared to reduce the risk of infection by between 30% and 84%, a result the company said was extremely unlikely to be due to chance alone.

The results are controversial because few non-white/non-Hispanic participants were included in the study: four of the 203 black volunteers (1.9%) and two of the 53 Asian participants (3.7%) who received the vaccine contracted HIV, compared with nine of the 111 blacks (8.1%) and two of the 20 Asians (10%) who received the placebo. "The company is claiming that this vaccine works better in African Americans and other non-Hispanic racial subgroups based on a difference of five people," noted Project Inform founding director Martin Delaney.

Reactions to the study results were mixed. "Last week, no human had ever been protected from HIV infection," said VaxGen president Donald Francis, MD. "This week, they

have." Said UNAIDS director Peter Piot, MD, PhD, "These results are promising. The trial provides clear evidence that a vaccine can work." But Seth Berkley, MD, of the International AIDS Vaccine Initiative (IAVI) called the results "disappointing," and Phill Wilson of the Black AIDS Institute said, "However promising this vaccine may look for black people, it is a promise for tomorrow."

NIAID director Anthony Fauci, MD, called the results "quite provocative, unexplained, and surprising." He said the federal government would perform laboratory tests on blood samples from trial volunteers to look for immune or genetic factors that may help explain why the vaccine seemed to work better in certain people of color. AIDS advocates have called on the National Institutes of Health (NIH) to conduct an independent review of the study data. VaxGen expects that results from a similar Phase III trial in injection drug users in Thailand will be available later this year.

PALLIATIVE CARE

In March the federal government issued new guidelines for palliative care for people with HIV disease. Palliative care refers to supportive measures aimed at preventing or easing pain and suffering. The document, "A Clinical Guide to Supportive and Palliative Care for HIV/AIDS," covers management of advanced HIV disease; psychosocial, cultural, and ethical issues; and end-of-life care. "This guide urges clinicians to treat not just the symptoms of this terrible disease, but to provide care that meets the physical, emotional, and spiritual needs of the individual," said Secretary of Health and Human Services Tommy Thompson. The guide is available at www.hab.hrsa.gov/tools/palliative.

NEW CLUES ABOUT HIV MUTATION AND ANTIBODIES

HIV mutates more rapidly than previously thought, according to research reported in the March 18, 2003 issue of the *Proceedings of the National Academy of Sciences.* Douglas Richman, MD, of the University of California at San Diego and colleagues found that the outer coat of HIV changes at an "incredibly rapid rate" in response to human antibodies. The researchers combined virus from HIV-infected individuals with luciferase (the light-emitting enzyme in fireflies) in order to visualize the virus as it replicates in antibody-containing blood plasma. They found that antibodies exert a "very strong selective pressure" on the virus, and that HIV mutates faster than the immune response can control it. "The bad news is that the virus is always staying a step ahead," said Dr. Richman.

In related news, George Shaw, MD, from Howard Hughes Medical Institute in Chevy Chase, Maryland, and colleagues reported in the March 20, 2003 edition of *Nature* that HIV continually changes the arrangement of sugar molecules in its outer envelope, which effectively blocks antibody attachment sites. This "glycan shield" helps the virus evade recognition and attack by antibodies, which can alter their own structure in response to a changing target but have trouble keeping up. Rapid viral evolution is the main impediment to developing effective anti-HIV treatments and vaccines.

Finally, Mario Clerici, MD, of the University of Milan and colleagues reported in the March 7, 2003 issue of *AIDS* that men who regularly have sex with HIV positive female partners yet remain uninfected have high levels of HIV-fighting antibodies in their semen. The study looked at 14 HIV negative men who had been having sex with an HIV positive woman partner for at least four years. Eleven of these men had relatively high levels of HIV-targeting IgA—a type of antibody found in bodily fluids that protects the entrances to the body—and antibody concentrations tended to be highest in the men who had recently had unprotected sex with their infected partners.

VIRAL HEPATITIS

Several reports at the Retrovirus conference looked at hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfection in people with HIV. Kelly Gebo, MD, from Johns Hopkins University in Baltimore (abstract 827) confirmed that HCV-related liver failure is now one of the major causes of death among people with HIV.

Results from a European multicenter study of 492 HIV/HCV-coinfected people (abstract 830) presented further evidence that HIV accelerates liver disease progression in people with hepatitis C. Shedding further light on this phenomenon, Jennifer Babik, MD, and colleagues from Stanford University in Palo Alto, California, reported in the February 2003 issue of the *Journal of Virology* that prolonged use of combination anti-HIV therapy in HIV/HCV-coinfected people is associated with a more genetically diverse population of HCV and higher HCV viral loads, both of which may accelerate hepatitis C disease progression.

For HIV/HBV-coinfected people, tenofovir continues to yield promising results. David Cooper, MD, of the University of New South Wales in Sydney and colleagues (abstract 825) presented data from Gilead study 903 showing that adding both tenofovir and 3TC to an existing anti-HIV regimen suppresses HBV replication better than 3TC alone.

Finally, new data were presented confirming that liver transplants can be successfully performed in people with HIV. Margaret Ragni, MD, from the University of Pittsburgh and colleagues from several transplant centers (abstract 155) found that HIV positive liver recipients have post-transplant survival rates similar to those of HIV negative recipients. Survival rates were 90.9%, 75.9%, and 75.9% at 12, 24, and 36 months, respectively. This study adds to the evidence that HIV status should no longer be considered a reason to deny someone a liver transplant.

GBV-C AND HIV

Several presentations at the Retrovirus conference confirmed that GB virus type C, or GBV-C (formerly known as

hepatitis G virus) may help prevent HIV infection and slow the progression of HIV disease. GBV-C is structurally related to the hepatitis C virus, but does not appear to cause disease. Carolyn Williams, PhD, of NIAID and colleagues looked at the effect of GBV-C coinfection in 271 men in the Multicenter AIDS Cohort Study (MACS). Analysis of blood samples from an early clinic visit (1–1.5 years after HIV infection) showed that 39% of the men had detectable GBV-C viral load and 46% showed evidence of past GBV-C infection and clearance. Looking at samples from a second visit 4–5 years later, men who had cleared GBV-C between the two visits were nearly six times more likely to have died, and men who were never infected with GBV-C were over two times more likely to have died, compared with men who remained GBV-C positive. After 11 years, about 75% of the men who remained GBV-C positive were still alive, compared with 39% of the persistently GBV-C negative men and 16% of those who cleared GBV-C. A Swedish team reported similar results (abstract 157). In their study of 230 HIV positive individuals, GBV-C was less common in people with AIDS (about 6%) than in those with asymptomatic HIV infection (about 30%), and participants who cleared GBV-C over the course of their illness (25%) had more rapid CD4 cell declines, a greater incidence of AIDS, and a higher risk of death. In yet another study (abstract 849), GBV-C positive individuals had lower HIV viral loads and higher CD4 cell counts, and responded better to anti-HIV therapy than those without GBV-C.

It is not clear how GBV-C exerts its protective effect, but it seems to help prevent HIV from infecting cells. GBV-C appears to decrease the amount of CCR5 receptors, which certain strains of HIV need to enter cells, and it seems to alter production of certain chemokines (including RANTES, MIP-1a, MIP-1b, and SDF-1) that occupy the same cell surface receptor binding sites used by HIV. "[T]here may be multiple mechanisms by which GBV-C may help people who have HIV infection," suggested Jack Stapleton, MD, of the Iowa City Veterans Administration Medical Center, whose team found that GBV-C inhibits HIV infection of white blood cells in the laboratory (abstract 156).

GBV-C is unlikely to be used as an HIV prophylaxis or treatment anytime soon. Aside from the ethical issue of introducing a new virus, researchers fear that injecting more GBV-C into people who already carry it could trigger an immune system response that clears the virus, leaving people with less protection than they started with. Further research is needed to understand how GBV-C and HIV interact, and whether this phenomenon could lead to the development of new anti-HIV therapies.

AIDS AND SARS

Public health officials have expressed concern that the latest global epidemic—severe acute respiratory syndrome, or SARS—might have a devastating effect on people with HIV/AIDS. SARS, which appears to be caused by a newly identified coronavirus (the same family as the virus that causes the common cold), is fatal in approximately 9% of cases. As of mid-June some 8,400 SARS cases had been reported worldwide, with nearly 800 deaths. Most cases have occurred in Asia, among health-care workers and close household contacts of affected patients. The exact route(s) by which the disease is spread remains unknown, and there is currently no known cure.

Intriguing reports from China, however, suggest that people with HIV/AIDS may be resistant to SARS. Early in the SARS outbreak in Guangzhou in southern China (where the new disease is believed to have originated), people with SARS and people with AIDS were housed in the same ward of one hospital. Although health-care workers tended patients with both diseases and several fell ill, none of the several dozen AIDS patients or their HIV positive visitors developed SARS.

Cheng Feng, MD, of the China/UK HIV/AIDS Project suggested the hypothesis that anti-HIV drugs may prevent infection with the SARS virus. David Ho, MD, of the Aaron Diamond AIDS Research Center in New York City and others are studying whether drugs used to treat HIV may also be effective against SARS. Another theory is that the lung damage associated with SARS may be due not to the virus itself, but rather to the immune system's excessive response. If this were the case, people with suppressed immune systems may be less likely to develop life-threatening SARS pneumonia. Interestingly, the most effective anti-SARS treatment to date is immunosuppressive steroid drugs.

NEW LIPODYSTROPHY DEFINITION

Researchers and physicians have long struggled over how to define the complex and variable set of fat abnormalities seen in HIV positive people taking antiretroviral therapy. Now, the HIV Lipodystrophy Case Definition Study Group has developed a model—published in the March 1, 2003 issue of *The Lancet*—that can be used to help diagnose the condition. Based on a study of 1,081 HIV positive individuals at 32 sites worldwide, the group developed a logistic regression model that includes ten variables: age, sex, duration of HIV infection, HIV disease stage, waist-to-hip ratio, anion gap (a blood electrolyte measurement that may signal acidosis), high-density lipoprotein (HDL, or "good" cholesterol) level, trunk-to-peripheral fat ratio, leg fat percentage, and intra-abdominal-to-extra-abdominal fat ratio. According to the researchers, this case definition is more sensitive and specific than definitions that rely on clinical observations alone. They hope the new model will "improve assessment of lipodystrophy prevalence, risk factors, and pathogenesis; [help devise] prevention and treatment approaches; and assist in diagnosis."

In related news, results published in the January 1, 2003 edition of the *Journal of Acquired Immune Deficiency Syndromes* suggest that severity of HIV disease, rather than use of antiretroviral drugs, may be the cause of lipoatrophy. The study, by Kenneth Lichtenstein, MD, of the University

of Colorado Health Sciences Center and colleagues, evaluated 546 participants in the HIV Outpatient Study (HOPS) in late 1998 and again in the summer of 2000. Those who had developed lipoatrophy between the two evaluations were compared with those who had not. The researchers determined that CD4 cell counts below 100 cells/mm^3 and HIV viral loads above 1,000 copies/mL were associated with fat loss. No association was seen between the use of any anti-HIV drugs and lipoatrophy. The authors concluded, "Our study suggests that HIV infection or factors associated with immune reconstitution may play a greater role in the development of lipoatrophy than the use of any specific medications."

HAART AND THE HEART

Several recent studies shed new light on cardiovascular disease (CVD) in people with HIV. Samuel Bozzette, MD, of the San Diego Veterans Administration Medical Center and colleagues reported in the February 20, 2003 issue of *NEJM* that anti-HIV drugs available since 1996—including PIs—do not appear to increase the risk of heart attacks or strokes, despite their association with high blood fat levels and insulin resistance. The researchers retrospectively looked at records from nearly 37,000 people with HIV (98% men) treated at U.S. Veterans Administration facilities between January 1993 and June 2001. They found that in addition to an expected overall decrease in mortality due to better anti-HIV therapies, since 1995 the rate of hospital admissions and deaths related to heart disease or stroke has also fallen. The authors concluded that the study indicated that there was "no relation between the use of nucleoside analogues, protease inhibitors, or non-nucleoside reverse transcriptase inhibitors and the hazard of cardiovascular or cerebrovascular events." However, they cautioned that eight years might not be long enough to determine the full side effects of HAART.

Others, however, have reached the opposite conclusion. At the Retrovirus conference Nina Friis-Møller, MD, from Hvidovre University in Copenhagen and colleagues (abstract 130) presented early results from the ongoing Data on the Adverse Events of Anti-HIV Drugs (DAD) study, the first prospective trial specifically designed to look at whether antiretroviral therapy is associated with heart disease. The analysis included 23,468 subjects (76% men) from 11 groups in Europe, Australia, and the U.S.; 81% were on some type of anti-HIV therapy. During the observation period there were 126 myocardial infarctions (heart attacks), 36 of them fatal—an incidence rate of 3.5 per 1,000 person-years. Older age, male sex, smoking (60% were current or former smokers), history of coronary heart disease (CHD), higher total cholesterol levels, diabetes, and use of antiretroviral therapy—but not triglyceride levels—were associated with an increased risk of heart attack. Surprisingly, people with self-defined lipodystrophy were less likely to have a heart attack in this study. The authors concluded that potent anti-HIV therapy was associated with a 26% increased risk of myocardial infarction per year of antiretroviral drug exposure. It is important to note that although the heart attack rate was higher in people taking anti-HIV drugs, the absolute risk remained low.

Similarly, Scott Holmberg, MD, and colleagues with the HOPS team reported in the November 30, 2002 edition of *The Lancet* that 19 out of 3,247 people (0.58%) taking PIs had a heart attack during the study period (January 1993 through January 2002), compared with 2 out of 2,425 individuals (0.08%) not taking the drugs. "Our findings suggest that, although infrequent, use of protease inhibitors is associated with increased risk of myocardial infarction in patients with HIV-1," the authors concluded. Most of those who had a heart attack in this study had other classic heart disease risk factors, including smoking, high blood pressure, high blood fat levels, and diabetes.

In the April 1, 2003 edition of *Clinical Infectious Diseases,* Colleen Hadigan, MD, of Massachusetts General Hospital in Boston and colleagues reported that the CHD risk in people with HIV appears to be related to patterns of body fat abnormalities. In their ten-year study, HIV positive individuals with fat abnormalities (both loss of peripheral subcutaneous fat and accumulation of visceral fat in the abdomen) had a "significantly elevated" calculated risk of CHD (using the Framingham Heart Study risk factor equation) compared with HIV negative Framingham Offspring Study participants matched for age, sex, and body mass index. However, the HIV positive participants did not have a greater calculated CHD risk than HIV negative individuals with a similar waist-to-hip ratio, and HIV-infected people without fat abnormalities did not have an elevated risk.

Looking at etiology (cause of disease), Eric Smart, PhD, of the University of Kentucky Medical School and colleagues reported in the February 1, 2003 issue of the *Journal of Clinical Investigation* that PIs may contribute to coronary artery disease independently of their effect on blood triglyceride and cholesterol levels. In Dr. Smart's study, mice given indinavir, ritonavir, or amprenavir developed early coronary artery disease even though their blood fat levels remained normal. The researchers also found increased levels of CD36 protein and cholesterol esters in the macrophages (a type of white blood cell) of mice who received PIs, a change often associated with atherosclerosis (the buildup of plaques in the arteries).

Mauricio Concho, MD, from the University of Miami and colleagues reported at the American Stroke Association conference in February that HIV positive people who had lipodystrophy syndrome related to PI use had more arterial plaques and greater thickening of the intima-media (inner and middle layers) of the carotid arteries in the neck, potentially leading to a greater risk of stroke. Two studies at the Retrovirus conference also looked at carotid intima-media thickness. Judith Currier, MD, of the University of California at Los Angeles and colleagues (abstract 131) found no difference in intima-media thickness between HIV-infected

people who used PIs, HIV-infected individuals with no previous PI use, and HIV negative people. But a prospective, longitudinal substudy by Priscilla Hsue, MD, of UCSF and colleagues (abstract 139LB) found that after one year, carotid intima-media thickening was accelerated in people with HIV and was associated with nadir CD4 cell counts below 200 cells/mm^3 and PI use.

In terms of treatment, Italian researchers reported in the April 11, 2003 issue of *AIDS* that fibrates and statins, drugs used to reduce high blood fat levels, are safe and effective in HIV positive individuals taking PIs. Clearly, more—and longer—research is needed to elucidate the true relationship between HIV disease, antiretroviral therapy, metabolic complications, and cardiovascular disease. In the meantime, Daniel Kuritzkes, MD, of Harvard Medical School recommended in a *NEJM* editorial accompanying Dr. Bozzette's article that people taking anti-HIV drugs should "use extra precautions to keep their blood vessels healthy"—including quitting smoking, maintaining a healthy weight, exercising, and taking lipid-lowering medications if indicated.

NEW U.S. HIV TESTING STRATEGY ANNOUNCED

In the April 18, 2003 issue of *Morbidity and Mortality Weekly Report* the U.S. Centers for Disease Control and Prevention (CDC) put forth a new initiative intended to increase the number of people tested for HIV. According to the report, "The HIV initiative emphasizes the use of proven public health approaches to reducing the incidence and spread of disease." Studies suggest that some two-thirds of people with HIV in this country do not know they are infected.

According to the new CDC recommendations (which are not legally binding on the states), HIV testing should become a routine component of medical care. In particular, pregnant women and newborns should be routinely tested unless they specifically request that HIV tests not be done. Testing should also be offered as part of regular medical appointments in areas of high HIV prevalence and to people whose backgrounds suggest they may be at risk. In addition, the recently approved OraQuick 20-minute HIV test should be made more widely available outside of medical settings, for example, in prisons and homeless shelters. In some cases the usual extensive pretest counseling may be reduced or eliminated.

The CDC also emphasized working with HIV-infected people to change their behavior to reduce their chances of transmitting the virus, and raised the controversial prospect of partner tracing and notification (which is done for most other sexually transmitted infections but has been limited in the case of HIV due to confidentiality issues). Advocates for people with HIV/AIDS have long expressed concern that mandatory testing or partner notification could drive people away from the health-care system, thus making it less likely that they will be tested or treated for HIV. Addressing such fears, National Center for HIV, STD, and TB Prevention director Howard Jaffe, MD, said, "Routine testing will be purely voluntary. It is not our intent to coerce people to have this testing done, or to stigmatize them if they decline. For those that do decide to have routine testing, the results will be kept strictly confidential."

HIV AND AIDS CASE RATES RISE

After falling for nearly a decade, the number of diagnosed AIDS cases in the U.S. rose slightly from 2000 to 2001, researchers reported at the Retrovirus conference. Though the increase was small—just 1%—public health officials are concerned because it represents the first rise since 1993.

Researchers also reported that the number of people testing HIV positive increased by 8% from 1999 to 2001 in the 25 states that report test results to the federal government. Ronald Valdiserri, MD, of the CDC reported that the number of HIV cases rose 14% among men who have sex with men during this period, compared with 8% for the population as a whole. About half of the new HIV cases were in women. Dr. Valdiserri acknowledged that this "statistical snapshot" might not be accurate, since it does not include states with large HIV/AIDS caseloads (including California and New York) that do not report new HIV infections. "It's only a single point in time, and we can't say it's a trend, but it is very worrying," he said.

The number of people living with HIV has increased over the past several years as the rate of new infections has remained steady but fewer people have died of AIDS since the introduction of new treatments in the late 1990s. While the rate of death due to advanced AIDS or AIDS-related OIs continues to fall, an increasing number of people with HIV are now dying of other causes, including lymphoma and end-stage liver disease, often related to hepatitis C coinfection.

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Lifestyle Habits That Contribute to Optimal Health

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

TMC114 and Other Investigational Drugs for Salvage Therapy

John Hawes

It is well known that highly active antiretroviral therapy (HAART) is effective for HIV positive people initiating treatment, and that suppression of HIV replication is durable in those who can tolerate potent multidrug anti-HIV therapy over long periods. In a recent study, the rate of viral breakthrough on treatment was 3.6 per 100 person-years, equivalent to one individual with viral breakthrough per 27.8 person-years of follow-up. (A person-year is a shorthand term used by epidemiologists to make comparisons.) This low rate of viral rebound and results from other research suggest that if viral suppression is achieved with initial treatment, and if adherence to therapy can be maintained, the chances of treatment failure are minimal. Yet antiretroviral therapy may still fail despite the availability of some 18 anti-HIV drugs, and the need for salvage, or "rescue," regimens remains urgent.

Although there have been concerns regarding drug development and progress in moving experimental candidates toward regulatory approval, new findings were presented for several investigational agents that show promise as part of future salvage regimens at the 10th Conference on Retroviruses and Opportunistic Infections, held February 10–14, 2003, in Boston. Speaking at the conference, John Mellors, MD, a virologist from the University of Pittsburgh, referred to the number of new compounds in the pipeline as a "bumper crop." Several of these agents are being investigated as therapies for treatment-experienced people with resistant virus.

TMC114

TMC114 is a second-generation protease inhibitor (PI) from Tibotec-Virco, a Belgian pharmaceutical company owned by Johnson and Johnson. The drug is designed to be active specifically against virus with PI-resistant mutations. Previous *in vitro* (laboratory) work has shown that TMC114 has potent activity against both wild-type (nonmutated) and PI-resistant HIV. Ritonavir (Norvir) enhances the effects of TMC114 *in vivo* (in humans), and coadministration of ritonavir may allow lower doses of TMC114 to be used. At the Retrovirus conference one oral and two poster presentations provided the latest *in vitro* and clinical results for this promising new compound.

The first clinical results for TMC114 in people with HIV were presented by Keikawus Arasteh, MD, from Vivantes Auguste-Viktoria-Klinikum in Berlin. In an open, randomized, two-week Phase II study, TMC114 was evaluated in 50 HIV positive participants who had previously taken multiple PIs and whose current PI-containing regimens were failing. Mean (average) baseline plasma viral load and CD4 cell counts were 20,000 copies/mL and 297 cells/mm^3, respectively. The mean number of primary PI mutations per participant was six, and nearly half had virus resistant to all available PIs. TMC114 plus low-dose ritonavir at one of three different dosages—300 mg/100 mg twice daily, 600 mg/100 mg twice daily, or 900 mg/100 mg once daily—was substituted for the failing PI in the regimens of 38 of the subjects, while 12 continued their current regimens; no other antiretrovirals were changed.

After 14 days an intent-to-treat analysis (which included all subjects according to the original randomization, even if they later switched therapy or dropped out) showed that TMC114/ritonavir reduced viral load by 90% in 70–90% of treated participants, depending on the dosage used. The twice-daily regimens outperformed the once-daily regimen. Decreases in viral load from baseline ranged from 0.47 to 2.49 log (mean of 1.35), and almost all participants (97%) who received TMC114/ritonavir had at least a 0.5 log (70%) drop in viral load. (See sidebar on page 15 for an explanation of logs.)

The most commonly reported adverse events were gastrointestinal (GI) symptoms; 32% of the participants experienced diarrhea—a much lower percentage than seen when TMC114 is given at higher dosages without ritonavir. Serious toxicities seen in the study were (reversible) liver inflammation in one person and severe liver enzyme elevations in five others receiving a TMC114/ritonavir regimen. Two people discontinued treatment, one due to GI discomfort and the other due to severe rash.

Two poster presentations at the conference provided new data on TMC114's *in vitro* potency against resistant virus and its clinical pharmacokinetics (action in the body) and safety when coadministered with ritonavir. The laboratory study tested TMC114 against HIV strains with mutations conferring resistance to the PIs ritonavir, saquinavir (Fortovase), indinavir (Crixivan), nelfinavir (Viracept), and amprenavir (Agenerase). The results showed that TMC114 not only blocked the infection of human CD4 cells by resistant virus, but also was active against multi-PI–resistant virus from people who had no response to any existing antiviral regimens. Analysis of the interaction of TMC114 with the HIV protease molecule revealed that TMC114 differs from existing PIs—perhaps due to the compound's highly flexible and adaptive nature—which may account for its potency against resistant virus.

John Mellors, MD, referred to the 44 different experimental anti-HIV compounds in the pipeline as a "bumper crop."

The second poster presented a study of different doses of TMC114 given with and without ritonavir to healthy, HIV negative volunteers for 14 days. The results showed that the minimum TMC114 concentrations and drug exposure over a 24-hour period were substantially increased when TMC114 was given with low-dose ritonavir—even when administered once daily at lower doses—compared with TMC114 used alone twice daily. The frequency of adverse events was reduced, however, in the volunteers who received TMC114 plus ritonavir compared with those who received higher-dose TMC114 alone. For those taking TMC114 alone, GI-related adverse events included diarrhea in 78%, vomiting in 17%, and nausea in 14%. For those taking TMC114/ritonavir, diarrhea was reported in 30% and nausea in 7.5%. These results suggest that the adverse effects of TMC114 may be lessened without any loss of potency through the coadministration of low-dose ritonavir.

The GI effects of TMC114 are largely attributable to a substance in its current formulation, polyethylene glycol. According to Richard Hoetelmans, PhD, the study's lead investigator, a tablet formulation without polyethylene glycol is being investigated, but results are not expected until 2004. The most effective and safest formulation and dose of TMC114 remain to be determined.

Overall, the results of these studies show that TMC114 used with low-dose ritonavir given either once or twice daily has promise as a new agent to treat PI-resistant HIV, and that further clinical testing should be pursued. More will be known about the future of this drug once the results of the planned 24-week trials using the tablet formulation are available. With PI resistance continuing to be a cause of treatment failure, these results will be closely watched.

Other Novel Investigational Agents for Salvage Therapy

New agents in development from existing antiretroviral drug classes appear to offer advantages over those currently in clinical use, such as less complex treatment regimens, increased efficacy against resistant virus, and less toxicity. However, cross-resistance within the PI and non-nucleoside reverse transcriptase inhibitor (NNRTI) classes may limit their impact, especially when compared with investigational drugs that act against new viral targets.

Oral and poster presentations on 44 different experimental anti-HIV compounds were presented at the Retrovirus conference. Of these, 32 involve novel approaches that are not related to any of the first three antiretroviral drug classes (nucleoside reverse transcriptase inhibitors [NRTIs], NNRTIs, and PIs); 15 are genetic or immune-based therapies. Below are brief summaries of the findings presented at the conference for several agents that may have potential as future treatment options for salvage therapy. (Note: none of the new genetic therapies, which are at a very early stage of development, are included.)

ENTRY INHIBITORS

Twelve presentations provided new data on experimental entry inhibitors, which include binding and fusion inhibitors. Agents in this class attempt to block HIV from entering host cells. The first drug in this class, T-20 (enfuvirtide, Fuzeon), was granted U.S. approval in March for use with other antiretrovirals in treatment-experienced people with persistent viral load despite ongoing anti-HIV therapy—in other words, as part of a salvage regimen. As with other antiretrovirals, however, resistance to T-20 has been observed. One study presented at the conference showed a mean 21-fold loss of susceptibility in those whose T-20 treatment failed. The development of new entry inhibitors remains a priority, and three of the more promising agents in this class are discussed below.

T-1249

The fusion inhibitor **T-1249** has a structure similar to that of T-20. Now in Phase II clinical trials, T-1249 appears to have 2 to 100 times greater potency than T-20, and is active against T-20–resistant virus. Like its predecessor, T-1249 inhibits fusion of HIV with host cells by binding to the gp41 protein on the virus' surface, but at a slightly different location, which is believed to account for T-1249's activity against T-20–resistant virus. Thus, it appears that T-1249 may be a useful option for some people whose HIV has developed resistance to T-20.

ABOUT LOGS

Viral load levels are customarily expressed in one of two ways: absolute numbers (e.g., 1,000 copies/mL) or logs (e.g., 3 log copies/mL).

A *log* is a way of expressing large numbers using the logarithmic scale. Simply put, a log refers to how many times a base number—10 in the case of viral load—is multiplied by itself to produce a given absolute number. For example, 3 log is the same as 10 x 10 x 10, which equals 1,000.

An easy way to remember the log system is to count the zeros in numbers that are expressed as powers of 10. The number of zeros equals the log value. For example, 1,000 (three zeros) equals 3 log, 100 (two zeros) equals 2 log, and 10 (one zero) equals 1 log. See the accompanying chart for other conversions from logs to absolute numbers.

A *log change* in viral load level reflects a 10-fold (exponential) increase or decrease. For example, a decrease in viral load from 1,000 to 100 copies/mL is a 1 log reduction, since the viral load has dropped from 3 log to 2 log copies/mL (3 log – 2 log = 1 log change). Note that the 1 log change does not represent a decrease in absolute numbers (a mere 10 copies/mL), but rather a 10-fold decrease. An increase from 100 to 1,000 copies/mL likewise would be a 1 log change.

Using more real-world figures, a person might begin treatment with a viral load of 62,376 copies/mL. Anti-HIV therapy might then reduce that person's viral load to 471 copies/mL. In approximate log figures, that is a reduction from about 4.8 log to about 2.7 log copies/mL, or a 2.1 log decrease (4.8 log – 2.7 log = 2.1 log change).

Log changes also can be expressed in terms of *percentages.* When thinking of increases and decreases in viral load levels, it might be useful to remember the following:

0.5 log change = 70% change in viral load (VL)

1 log change = 90% change in VL

2 log change = 99% change in VL

3 log change = 99.9% change in VL

LOGS AND ABSOLUTE NUMBERS

log copies/mL	log copies/mL	log copies/mL	log copies/mL	log copies/mL	log copies/mL	log copies/mL
	1.0 = 10	**2.0 = 100**	**3.0 = 1,000**	**4.0 = 10,000**	**5.0 = 100,000**	**6.0 = 1,000,000**
0.1 = 1	1.1 = 13	2.1 = 126	3.1 = 1,259	4.1 = 12,589	5.1 = 125,893	6.1 = 1,258,925
0.2 = 2	1.2 = 16	2.2 = 158	3.2 = 1,585	4.2 = 15,849	5.2 = 158,489	6.2 = 1,584,893
0.3 = 2	1.3 = 20	2.3 = 200	3.3 = 1,995	4.3 = 19,953	5.3 = 199,526	6.3 = 1,995,262
0.4 = 3	1.4 = 25	2.4 = 251	3.4 = 2,512	4.4 = 25,119	5.4 = 251,189	6.4 = 2,511,886
0.5 = 3	1.5 = 32	2.5 = 316	3.5 = 3,162	4.5 = 31,623	5.5 = 316,228	6.5 = 3,162,278
0.6 = 4	1.6 = 40	2.6 = 398	3.6 = 3,981	4.6 = 39,811	5.6 = 398,107	6.6 = 3,981,072
0.7 = 5	1.7 = 50	2.7 = 501	3.7 = 5,012	4.7 = 50,119	5.7 = 501,187	6.7 = 5,011,872
0.8 = 6	1.8 = 63	2.8 = 631	3.8 = 6,310	4.8 = 63,096	5.8 = 630,957	6.8 = 6,309,573
0.9 = 8	1.9 = 79	2.9 = 794	3.9 = 7,943	4.9 = 79,433	5.9 = 794,328	6.9 = 7,943,282
copies/mL refers to viral load						**7.0 = 10,000,000**

The results from a planned interim analysis of a trial sponsored by Roche/Trimeris, the pharmaceutical partnership developing T-1249, were presented at the conference. The study evaluated T-1249 (192 mg once daily) in 25 participants taking failing regimens containing T-20 (i.e., two consecutive plasma viral load measurements between 5,000 and 500,000 copies/mL). At the time of switching from T-20 to T-1249, mean viral load was 100,000 copies/mL. Twenty-four of these heavily pretreated participants had T-20–resistant virus, as revealed by genotypic resistance testing.

The interim results showed that in the first 25 participants who completed the ten-day study, approximately two-thirds experienced decreases in viral load of at least 1 log (90%). No subjects discontinued the study, and no serious adverse events considered related to T-1249 were reported. The results also showed that the longer people received T-20 after the detection of virological failure, the less response they had to T-1249, most likely due to the increasing development of cross-resistance during persistent viral replication. This suggests that T-20 should be stopped as soon as

possible if resistance develops in order to preserve the benefit of T-1249.

Like T-20, T-1249 must be given via subcutaneous (under the skin) injection. It appears that T-1249 injections can be given once daily, compared with twice daily for T-20, but four separate injections will be required with each administration.

TNX-355

Another entry inhibitor in clinical trials is the anti-CD4 monoclonal antibody **TNX-355** (formerly Hu5A8), produced by Tanox. These antibodies (immune system proteins that recognize foreign substances) are genetically engineered to attach to the CD4 receptors on the surface of T cells, thereby preventing the entry of HIV into the host cell.

TNX-355 is currently in Phase I testing. Results of a short-term, single-dose, dose-ranging study of TNX-355 in 30 treatment-experienced HIV positive participants, 19 of whom were receiving a failing regimen, were presented at the conference by Daniel Kuritzkes, MD, a virologist at Brigham and Women's Hospital and Harvard Medical School in Boston. The study found that decreases in HIV plasma viral load occurred at all doses of TNX-355 tested (1, 3, 10, and 25 mg/kg) and, as expected, the higher doses were associated with better virological response (lower viral load). Ten of the 12 participants who received the higher doses had significant drops in viral load, with peak reductions occurring 2–3 weeks after the single dose. Viral load decreased as much as 97% in some participants. No decrease in the number or function of CD4 cells was detected, and no serious adverse events were noted.

Like the fusion inhibitors T-20 and T-1249, TNX-355 also must be given by injection (although T-20 and T-1249 are given subcutaneously, while TNX-355 is infused intravenously, or directly into a vein). However, unlike the Roche/Trimeris drugs, which are administered daily, TNX-355 may need to be given only once every 2–3 weeks. The optimal dose and the duration of TNX-355's effects remain to be determined, and a multiple-dose study is planned.

UK-427,857

In vitro and early clinical results were presented at the Retrovirus conference for **UK-427,857,** an entry inhibitor that works by blocking HIV from attaching to a coreceptor called CCR5 that the virus uses to enter many host cells. The compound is currently in Phase I clinical testing. The *in vitro* results showed that UK-427,857 has potent activity against the HIV subtype most common in the U.S. (subtype B), as well as those commonly found in other parts of the world (subtypes A, C–G, J, and O), including Africa and Asia.

Preliminary clinical data also appear encouraging. Results of a dose-ranging, pharmacokinetic study in healthy, HIV negative volunteers showed that UK-427,857 can be given orally, is rapidly absorbed, and has a good safety profile—at least so far. Importantly, UK-427,857 does not seem to promote heart problems. (In early studies it appeared that some other CCR5 blockers—such as Schering-Plough's **SCH-C**—might increase the risk of irregular heartbeat.) As with many other investigational agents in early trials, the dose of UK-427,857 that will be used in future efficacy and safety studies has not yet been determined.

INTEGRASE INHIBITORS

The HIV integrase enzyme is responsible for inserting the virus' genetic material into the host cell's DNA (known as integration), thereby employing the cell's machinery for viral replication. Several experimental compounds inhibit this step in the viral lifecycle. Although no clinical data were presented at the Retrovirus conference on the two agents furthest along in development—**L-708,906** and **S-1360,** both of which are diketo (or diketobutanoic) acids currently being tested in humans—results from *in vitro* studies show that there may be a significant potential for cross-resistance among the diketo compounds, and that other types of integrase inhibitors with distinct resistance profiles should also be investigated.

Based on data presented at the conference, one solution may be the pyranodipyrimidine (PDP) integrase inhibitors, which are structurally different from the diketo compounds. Early findings with **V-165,** a PDP agent being developed by the Rega Institute in Belgium, suggest that this compound inhibits both the reverse transcription step and the HIV integration step—a level of activity beyond that exhibited by the two leading integrase inhibitor candidates. In addition, V-165 was reported to be active *in vitro* against viral strains that are resistant to diketo compounds. These results are promising, but preliminary.

BUDDING INHIBITORS

Early preclinical results from a study of **PA-457,** an agent from a new class of antiretrovirals called budding inhibitors, were presented at the conference by researchers from Panacos Pharmaceuticals. PA-457 appears to interrupt later stages of the HIV lifecycle, when newly produced viral proteins are packaged into new virus particles (virions) as they leave the infected host cell through the cell membrane—a process called budding. How exactly PA-457 inhibits this process is unknown.

In laboratory tests PA-457 showed potent activity against all HIV isolates, including those highly resistant to NNRTIs and PIs. The compound was also found to act synergistically (with enhanced effects) with AZT (zidovudine, Retrovir), nevirapine (Viramune), and indinavir, which together represent the first three major classes of approved antiretrovirals.

Finally, PA-457 was orally bioavailable (able to be taken by mouth) in an animal model. Based on study results to date, the manufacturer intends to proceed with further development of this compound.

Conclusion

Effective and less toxic salvage therapy options for people with HIV remain a pressing need, as existing drug regimens continue to fail due to resistance and less-than-optimal adherence, with its ensuing loss of potency. Thus, the ongoing development of second-generation antiretroviral agents, including those that interfere with new steps in the HIV lifecycle, is crucial for broadening and improving treatment for those with limited therapeutic options. Although history indicates that most of the experimental compounds presented at the Retrovirus conference will never attain FDA approval, it is heartening to see so much interest and progress on the part of the pharmaceutical industry in identifying and developing novel agents.

For information on currently enrolling studies of new anti-HIV agents, see Clinical Trials on page 44 of this issue.

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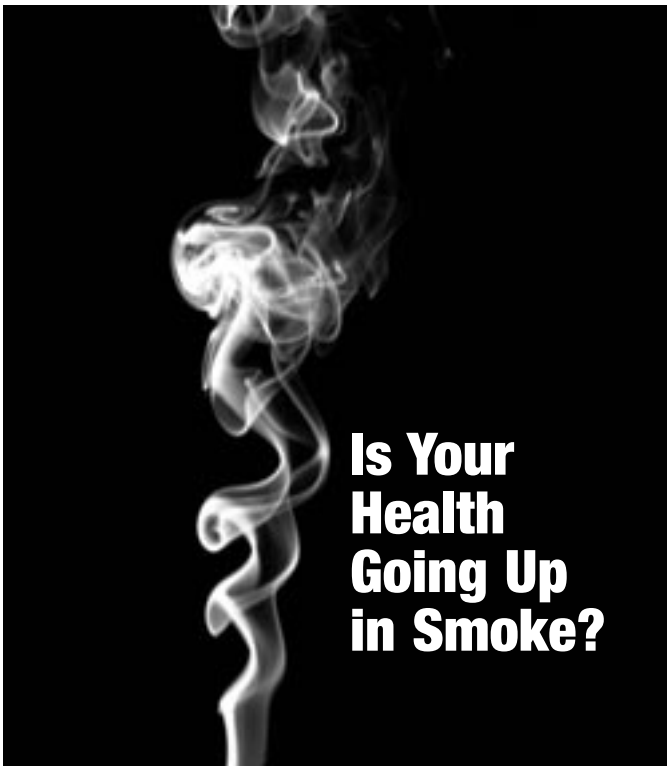

Smoking is a habit. It is often a stress-related activity. Smoking is also a risk factor for many diseases that affect people with HIV, including cardiovascular disease, bone disease, and anal cancer.

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.

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.

Learn more about the art of quitting. There is no better time than now.

Non-Hodgkin's Lymphoma

The use of highly active antiretroviral therapy (HAART) and effective prevention and treatment strategies for opportunistic illnesses (OIs) have dramatically increased survival for people with HIV disease. As a result, there is a growing focus on serious complications that may arise during the course of illness, including AIDS-associated malignancies (cancers). Current AIDS-defining malignancies include Kaposi's sarcoma (KS), primary central nervous system (CNS) lymphoma, systemic non-Hodgkin's lymphoma (NHL), and invasive cervical cancer. This article will review systemic NHL.

Amir Goldkorn, MD

What Is Non-Hodgkin's Lymphoma?

Lymphoma is a cancer characterized by rapidly dividing, abnormal lymphocytes, which are white blood cells that comprise part of the immune system. One type of lymphoma, Hodgkin's disease, has a unique appearance under the microscope, as well as a typical clinical course and treatment. All other types are collectively termed non-Hodgkin's lymphoma. Only NHL is currently considered to be an AIDS-defining illness, though there is accumulating evidence that Hodgkin's disease may also occur with increased frequency in HIV-infected individuals.

While HAART has reduced the rate of OIs in people with HIV, its overall effect on the incidence of NHL is not clear. NHL occurs in approximately 5–10% of HIV positive individuals, typically late in the course of their disease. Due to this late presentation, NHL is the AIDS-defining diagnosis in only 3% of AIDS cases, but eventually accounts for up to 16% of AIDS-related deaths.

Although the precise cause of NHL is unknown, multiple studies have shown that compared with the general population, HIV positive individuals have a 200- to 600-fold increased risk of developing NHL, particularly the more aggressive subtypes. This much higher incidence in the HIV positive population is attributed to two main causes. The first has to do with altered immune function. Reduced numbers of functional CD4 cells in people with HIV leads to impaired immune surveillance, or failure to recognize and destroy abnormally multiplying cells. In addition, there is evidence that several lymphocyte-signaling molecules—such as interleukin 6 (IL-6), interleukin 10 (IL-10), and

chemokine receptor 5 (CCR5)—play a role in the development of NHL in people with HIV, possibly due to abnormal stimulation of cell proliferation (rapid reproduction or replication).

The second main cause of increased NHL in people with HIV has to do with the role of viruses. Continuously multiplying HIV constitutes a chronic (long-term) stimulus for proliferation and activation of lymphocytes. Over time, this constant lymphocyte hyperactivity may progress to an unchecked, cancerous state. In addition, HIV viral genes have been found to integrate into the DNA (genetic material) of human macrophages, another type of white blood cell, thereby inducing these immune cells to overproduce signals that stimulate lymphocytes. Finally, other viruses—such as Epstein-Barr virus (EBV, the cause of mononucleosis) and human herpesvirus 8 (HHV-8, associated with KS)—also have been implicated in certain subtypes of NHL, though their exact roles remain unclear.

NHL Classification

Although the malignant, or cancerous, cell type in NHL may be either B cells (lymphocytes that produce antibodies) or T cells (lymphocytes that attack infected or cancerous cells directly), the overwhelming majority of NHL in people with HIV is of the B cell type.

Traditionally, the different types of NHL have been classified according to the Working Formulation proposed in 1982, which categorizes lymphomas according to the appearance of the malignant cells (small-cleaved vs large), their growth pattern in lymph nodes (follicular vs diffuse), and the aggressiveness with which they multiply and spread (low, intermediate, or high grade). Thus, a low-grade, follicular, small-cleaved B cell lymphoma would have a more indolent, or slow, course than an intermediate-grade, diffuse (widespread), large cell lymphoma.

Over the past two decades, new technologies have enabled more sophisticated characterization of malignant lymphocytes beyond simply describing their appearance under the microscope. Specifically, immunophenotyping and flow cytometry are techniques that identify specific marker molecules, such as CD4 and CD20, found on the cell surface of lymphocytes. By identifying the specific surface marker signatures of various lymphomas, and also by detecting certain chromosomal (genetic) abnormalities specific to these lymphomas, it is now possible to tease apart types of NHL which previously had been lumped together due to their similar appearance under the microscope, but which are actually separate disease entities with different clinical courses and prognoses. Thus, the new Revised European-American Lymphoma Classification and World Health Organization (REAL/WHO) system now includes 23 subtypes of B cell and T cell NHL.

Most common among the HIV positive population are the more aggressive (intermediate- and high-grade) subtypes such as Burkitt's lymphoma, diffuse large cell lymphoma, immunoblastic lymphoma plasmacytoid, and anaplastic large B cell lymphoma. Only the high-grade, more aggressive forms of NHL are considered AIDS-defining, though individuals with HIV may have an increased risk of low-grade NHL as well.

Clinical Presentation

The most common symptoms heralding the onset of NHL in people with HIV are the so-called B symptoms, which consist of unexplained fevers, drenching night sweats, weight loss (more than 10% of normal body weight), and fatigue. If lymphoma cells take hold and grow in the peripheral lymph nodes, such as those in the neck or groin, the individual may begin to notice painless, firm, enlarging lumps in these areas. As noted above, people with HIV tend to develop the more aggressive, high-grade subtypes of NHL. For this reason, approximately two-thirds of individuals already have widely spread (late-stage) disease at the time of diagnosis, with up to 90% presenting with extranodal lymphoma (i.e., lymphoma that has progressed beyond the lymph nodes).

The most frequently involved extranodal site (in up to 33% of people) is the bone marrow, where white and red blood cells and platelets (cells that assist in blood clotting) are produced. When lymphoma cells infiltrate the bone marrow, they displace the normal precursors of white cells, red cells, and platelets, leaving no room for normal blood cell development. As a result, a person presenting with bone marrow involvement may have a low white blood cell count (contributing to increased risk of infection), a low red blood cell count (anemia, contributing to fatigue and breathlessness), and/or a low platelet count (contributing to easy bruising or bleeding).

The gastrointestinal tract (stomach and intestines) and liver are involved in approximately one-quarter of NHL cases, leading to symptoms such as bloating, abdominal pain, loss of appetite, nausea and vomiting, constipation or diarrhea, and jaundice (yellowing of the skin and whites of the eyes). Lymphoma in the rectum may occur, and present as a local mass or pain on defecation. A work-up (thorough diagnostic examination) of any new rectal mass in a person with HIV, especially if other systemic symptoms are present, should include a biopsy (removal of tissue for study) prior to excision (total removal) to rule out the possibility of lymphoma.

Central nervous system (CNS) involvement is found in approximately 20% of HIV positive people with NHL at the time of diagnosis. In these cases, malignant lymphocytes typically are found within the cerebrospinal fluid (CSF) in the meninges, the membranes that encase the brain and spinal cord. CNS involvement is frequently asymptomatic, but a person may experience headaches, back pain, nausea, and sensitivity to light, similar to the symptoms of infectious meningitis (inflammation of the meninges). In cases of more aggressive CNS involvement, lymphomatous masses may become

implanted in the meninges, or they may invade the brain itself, leading to more significant symptoms such as altered mental status and facial weakness or paralysis. [Ed. note: CNS involvement in NHL is distinct from primary CNS lymphoma, which originates as a mass in the brain or spinal cord and is usually associated with the Epstein-Barr virus. Unlike NHL, primary CNS lymphoma generally does not occur in people with more than 50 CD4 cells/mm^3.]

NHL Diagnosis and Staging

Typically, a person with HIV/AIDS might present to a health-care provider with some combination of the symptoms described above, for example, intermittent fevers and night sweats, fatigue, abdominal bloating, and an enlarged lymph node in the neck. The diagnosis of NHL is made with a needle biopsy of the lymph node, followed by microscopic examination and flow cytometric analysis of the tissue sample by a pathologist (a specialist who identifies diseases by examining cell and tissue samples).

If a needle biopsy does not reveal the presence of lymphoma, the node should be excised (removed) and examined to definitively rule out lymphoma. If there is no enlarged lymph node readily visible for biopsy, imaging studies may be done, such as a chest x-ray or a computed tomography (CT) scan of the chest and abdomen. If imaging reveals enlarged internal lymph nodes or masses, then a biopsy is performed guided by CT or ultrasound.

After the pathologic tissue diagnosis of NHL is made, the clinical stage of the disease must be determined. More advanced stages portend a worse prognosis (prospect of recovery and survival) and require more aggressive treatment. The Ann Arbor staging system is a scheme initially devised for staging Hodgkin's lymphoma, but it applies to NHL as well. It is based on the concept that lymphoma cells spread first through the lymphatic system to various lymph node groups, and from there to extranodal organs. Thus, there are four stages that correspond to increasingly distant spread of disease and worse clinical prognosis:

Stage I refers to NHL found in only one lymph node region—for example, an enlarged neck lymph node—but no other disease.

Stage II refers to disease involving two or more lymph node regions on the same side of the diaphragm (the large sheet of muscle that separates the chest cavity from the abdominal cavity), for example, enlarged lymph nodes in both the neck and chest.

Stage III disease involves lymph node groups on both sides of the diaphragm, for example, in the neck and groin.

Stage IV refers to widely spread disease that involves other organ systems, such as the CNS, the bone marrow, or the gastrointestinal tract.

To determine disease stage, several tests are performed at the time of diagnosis. CT scans of the chest, abdomen, and pelvis help to determine the extent of involvement of lymph nodes and extranodal organs. A bone marrow biopsy is performed to look for malignant lymphocyte infiltration. Under local anesthesia, a biopsy needle is inserted into the posterior iliac spine (the back of the pelvis) and a small amount of marrow is withdrawn and examined under a microscope for the presence of malignant lymphocytes. Similarly, a lumbar puncture (spinal tap) is performed to look for CNS disease. Again under local anesthesia, a needle is inserted into the space surrounding the spinal cord at the level of the lumbar spine, and a small amount of CSF is withdrawn and examined microscopically for the presence of malignant cells.

The blood level of lactate dehydrogenase (LDH) is checked, as this enzyme, produced by rapidly dividing lymphocytes, provides a prognostic index that reflects disease burden (i.e., how extensively the lymphoma has spread). Also, uric acid levels are checked, because this byproduct of lymphocyte proliferation can potentially cause kidney failure. Finally, all patients undergo basic blood tests to determine levels of white and red cells and platelets, as well as to assess liver and kidney function.

Two other tests are typically performed at the time of diagnosis, but these are done for treatment-related reasons rather than for staging purposes. The first is a functional imaging study, either a gallium-67 scan or positron emission tomography (PET). For these tests, the individual is first injected with a harmless radioactive substance that is taken up by cells with very high metabolic rates, including rapidly dividing malignant lymphocytes. These areas of uptake then light up on the scan, showing the location of the lymphoma. The gallium-67 or PET images complement the CT scans and serve as a useful baseline for disease location.

Often after NHL is treated, repeat CT scans reveal residual masses in lymph nodes or extranodal organs. This does not necessarily mean that treatment has failed. In some cases, although all the malignant lymphoma cells have been eliminated, residual scarring and swelling remain, which a CT scan cannot differentiate from actual lymphoma. Here lies the utility of a functional study. When the gallium-67 or PET scan is repeated, the masses noted on the CT scan can be checked for radioactive uptake. If these areas continue to light up, as they did in the baseline functional study, then the residual masses indeed represent

One of the most promising new approaches to NHL treatment is the use of immunotherapy.

persistent lymphoma. On the other hand, if the masses do not light up, then the residual areas noted on the CT scan can safely be regarded as simple scarring, not persistent disease.

The second test that may be performed for treatment purposes is an echocardiogram (ECHO), a noninvasive imaging method that uses ultrasound to visualize the chambers of the heart and to ensure normal contractile function. One class of chemotherapeutic drugs used to treat NHL—the anthracycline class, specifically doxorubicin (Adriamycin)—can cause cumulative damage to heart muscle. For this reason, a baseline ECHO is done prior to initiation of therapy (see below). While it is often acceptable to forgo an ECHO in young, otherwise healthy individuals, this study is essential in older people and those with known cardiac disease, or whenever there is doubt regarding a person's baseline cardiac function.

Favorable prognostic factors in HIV positive NHL patients include a CD4 cell count greater than 100 cells/mm³, age below 35 years, a normal LDH level, early disease stage at diagnosis, good performance status, no history of a prior AIDS-defining illness, use of HAART, and an adequate initial response to therapy.

NHL Treatment

The approach to treating NHL in people with HIV largely depends on its grade and stage. As previously noted, the overwhelming majority of NHL in people with HIV consists of intermediate- to high-grade aggressive disease. Accordingly, the majority of existing data, and most of the discussion in this article, pertain to this type of disease rather than low-grade NHL, which is relatively less common in people with HIV.

Briefly, low-grade NHL has a more indolent nature and is associated with longer survival. Paradoxically, because low-grade NHL cells grow and divide more slowly, they are relatively resistant to chemotherapy, which kills only rapidly dividing cells. Stage I or II low-grade NHL, which is localized by definition, can be treated with radiation therapy. Radiation produces up to a 50% relapse-free survival rate at 10–15 years in the HIV negative population. Treatment for stage III or IV low-grade NHL ranges from simple observation, to single agent chemotherapy, to full-strength combination chemotherapy.

Localized stage I or II intermediate- or high-grade disease historically has been treated only with local radiation therapy. In this procedure, a radiation oncologist (cancer specialist) carefully maps out and marks the region of the body that contains the lymphoma, and this field is then irradiated using a machine resembling an x-ray scanner that emits a strong beam of radiation. Daily sessions last approximately 15 minutes, and the full course is given over a period of 3–4 weeks. More recent studies have shown that combining radiation with chemotherapy leads to improved response and survival rates. Thus, the current standard of care for stage I or II intermediate- and high-grade NHL is radiation therapy along with a short course of combination chemotherapy, typically the CHOP regimen.

The CHOP regimen consists of four drugs: ***c***yclophosphamide (Cytoxan, Neosar), ***h***ydroxydaunorubicin (doxorubicin), vincristine (***O***ncovin), and ***p***rednisone. CHOP is typically given every three weeks. On the first day of each 21-day cycle, cyclophosphamide, doxorubicin, and vincristine are infused intravenously (into a vein) over several hours. Prednisone is given orally on days 1 through 5. Over the next three weeks, the patient is monitored for signs of infection and for significant drops in blood cell counts, and side effects such as nausea are treated until the cycle repeats.

While the optimal treatment for stage I and II NHL consists of three cycles of CHOP along with radiation therapy, treatment for stage III and IV disease relies on chemotherapy alone, since the lymphoma is too widespread to be included in a radiation treatment field. Over the years, multiple studies in the HIV negative population have investigated a variety of chemotherapy regimens, but none have been shown to improve upon the survival benefits of CHOP. Thus, the current standard of care for stage III and IV intermediate- to high-grade NHL in people with HIV consists of six cycles of CHOP. However, the question as to whether other regimens are more effective in this population is still under investigation. (See Clinical Trials on page 49 of this issue for currently enrolling studies.) Occasionally, the six cycles of CHOP are followed by a course of local radiation therapy to sites of residual disease. If CNS involvement is documented or strongly suspected, another chemotherapeutic agent—either methotrexate or cytarabine (Cytosar-U, DepoCyt)—is infused intrathecally into the CSF (similar to a lumbar puncture) once weekly for four weeks.

Treatment Toxicities and Complications

The most common side effects of treatment are the toxicities caused by chemotherapy and radiation. With respect to CHOP, the main toxicities of cyclophosphamide include bone marrow suppression (resulting in low white and red blood cell and platelet counts), nausea and vomiting, hair loss, and (rarely) urinary bladder inflammation.

Toxicities of doxorubicin include bone marrow suppression; nausea and vomiting; hair loss; irritation of the gastrointestinal mucosa (mucous membranes); and cumulative, dose-related heart muscle damage. The lifetime dose of doxorubicin cannot exceed a specific limit, beyond which there is a serious risk of heart failure.

The main toxicity associated with vincristine is peripheral neuropathy, which can manifest as numbness or tingling in the hands and feet. Prednisone's side effects include bloating, fluid retention, sleep disturbances, psychosis, elevated blood sugar, and gastritis (inflammation of the stomach lining).

The side effects of local field radiation depend on the area being irradiated, but generally include local skin and mucous membrane inflammation, gastrointestinal distress (e.g., diarrhea), and possibly bone marrow suppression.

Tumor lysis syndrome (TLS) is another concern when starting chemotherapy, especially in people with stage III or IV lymphoma and a heavy disease burden. The rapidly dividing malignant lymphocytes are often exquisitely sensitive to chemotherapeutic drugs, and many millions of these cells may die and rupture, or lyse, in the first hours of chemotherapy. Like all cells, lymphocytes contain high levels of potassium, phosphorus, and uric acid. These products are released into the bloodstream in large amounts when the lymphocytes rupture, potentially leading to electrolyte disturbances that can cause irregular heartbeat, kidney failure, and death if left untreated.

In people with a heavy disease burden at diagnosis, measures should be taken before and during chemotherapy to avoid TLS. Allopurinol (Zyloprim), a drug that inhibits the production of uric acid, may be started a few days before chemotherapy. During chemotherapy, copious intravenous fluids are given to wash out and rapidly eliminate the accumulating TLS products. Bicarbonate is also sometimes given to alkalinize the blood and urine, facilitating elimination. Finally, in people at high risk for TLS, blood electrolyte levels are checked frequently to monitor and rapidly correct any abnormalities.

Immune suppression due to chemotherapy is perhaps the treatment-related issue that has received the most attention in people with HIV. As described previously, one of the major side effects of most chemotherapeutic agents is bone marrow suppression, which may cause a drop in levels of white blood cells, specifically neutrophils that fight infection. Neutropenia (low neutrophil count) following chemotherapy results in greater vulnerability to infection, especially in HIV positive people who are already immunocompromised. Thus, in the pre-HAART era, up to 50% of NHL deaths in people with HIV were attributable to treatment-related OIs. To address this problem, several clinical trials were performed comparing the standard CHOP regimen with less immunosuppressive, reduced-dose chemotherapy regimens. These studies demonstrated that lower chemotherapy doses indeed caused less neutropenia and were just as effective in terms of survival.

The HAART era has brought a return to full-dose chemotherapy regimens such as CHOP for people with HIV. HAART increases CD4 cell counts, reduces HIV viral load, decreases the risk of OIs, and often leads to immune reconstitution. Because of these immune-boosting effects, rates of OIs in people on HAART who receive full-dose chemotherapy have decreased dramatically. Thus, the current standard of care is to integrate HAART with full-dose chemotherapy as early as possible in the treatment of NHL, while keeping in mind possible antiretroviral toxicities. For example, AZT (zidovudine, Retrovir) can suppress the production of neutrophils to such an extent that it may be preferable to substitute another anti-HIV drug for the duration of chemotherapy.

The current standard of care is to integrate HAART with full-dose chemotherapy as early as possible in the treatment of NHL.

Several other measures may be taken to minimize the risk of infection. Immediately after the completion of chemotherapy, subcutaneous injections of granulocyte colony-stimulating factor (GCSF, filgrastim, Neupogen) may be given. GCSF is a natural hormone that stimulates the production of neutrophils. Regular use of GCSF in people with HIV after chemotherapy for NHL helps to reduce the incidence of neutropenia and fever, as well as the length of hospital stays. It also allows for fewer reductions in chemotherapy doses and fewer treatment delays. Antibiotic prophylaxis (preventive treatment) against *Pneumocystis carinii* pneumonia (PCP) also should be provided to all HIV positive individuals receiving chemotherapy for NHL. Antimicrobial prophylaxis against *Mycobacterium avium* complex (MAC) should be given to those with CD4 cell counts below 50 cells/mm^3.

Prognosis for NHL

Large retrospective studies in the general population have identified several key factors that determine good response to therapy and favorable overall prognosis. These factors, which comprise the International Prognostic Index (IPI), include age below 60 years, LDH enzyme levels within normal limits, early disease stage, no more than one site of extranodal disease, and a good overall performance status (ability to carry out activities of daily life). In the HIV *negative* population, stage I NHL and a favorable IPI is associated with a five-year overall survival rate of 94%. Stage II NHL and one poor IPI risk factor is associated with a five-year overall survival rate of 70%. Stage I or II NHL with three poor IPI risk factors reduces the five-year overall survival rate to 50%. Stage III and IV NHL have a five-year overall survival rate of 50%, but this drops with additional poor IPI risk factors.

The prognosis for NHL in people with HIV is worse than that for the HIV negative population because the former

generally present with high-grade, aggressive, late-stage disease. Favorable prognostic factors in HIV positive NHL patients include a CD4 cell count greater than 100 cells/mm^3, age below 35 years, a normal LDH level, early disease stage at diagnosis, good performance status, no history of a prior AIDS-defining illness, use of HAART, and an adequate initial response to therapy.

Unfortunately, even among those who initially have a complete response to NHL therapy (up to 70% in people with HIV), 25% experience relapse (return of illness) within six months. In the pre-HAART era, this translated into an average survival period of 5–8 months. Since the introduction of HAART and the return to full-dose chemotherapy, several studies looking at various regimens have found improved average survival times, ranging from 18 months to as long as 53 months, though such results have not been consistently borne out in larger clinical trials.

For those who relapse or do not respond to initial treatment, the prognosis is grim. A variety of more potent, experimental chemotherapy regimens have been investigated, but these are associated with significantly increased toxicities. Whether such therapies in conjunction with HAART will improve the outlook for HIV positive people with relapsed or refractory (treatment-resistant) NHL is not yet known.

On the Horizon

Clearly, the poor prognosis of NHL in people with HIV demands continued exploration of new treatments. One of the most promising approaches is the use of immunotherapy. The most well-known and effective of these—already widely used in the HIV negative population—is rituximab (Rituxan), a human/mouse hybrid antibody that targets the CD20 antigen found on the surface of up to 95% of NHL lymphocytes. Studies reported in 2002 demonstrated that in the HIV negative population, the addition of rituximab to CHOP increased the complete response rate as well as overall survival in elderly patients. A similar large trial in people with HIV has recently been completed and results are expected to be presented later this year.

Variations on the anti-CD20 antibody theme are also in development. Tositumomab (Bexxar) and ibritumomab tiuxetan (Zevalin) are anti-CD20 antibodies linked to radioactive agents. When they bind to malignant lymphocytes, their radioactivity helps to destroy the cells. At present, their use in individuals with HIV remains investigational.

Another novel tactic for treating NHL in people with HIV is the use of high-dose chemotherapy followed by autologous (self-derived) bone marrow transplantation, or auto-BMT. The first step in this procedure is the collection of stem cells—bone marrow precursor cells that give rise to all white and red blood cells and platelets—from a patient. After the stem cells are collected and stored, the patient receives extremely high doses of chemotherapy aimed at eradicating the lymphoma. The chemotherapy doses are so strong that the bone marrow is completely destroyed, leaving the person with no means of producing white and red blood cells and platelets. Normally this would lead to the patient's rapid demise, but auto-BMT allows the individual's previously stored stem cells to be reinfused, after which they reconstitute the bone marrow and begin to produce new white and red cells and platelets. The strategy of auto-BMT therefore enables the use of much higher doses of chemotherapy than would otherwise be tolerated. The procedure already is commonly used in HIV negative patients. Recent small studies in people with HIV have demonstrated that this approach is also feasible in this population, and may extend survival times.

Other novel therapies are showing promise. Interleukin 12 (IL-12), a cytokine, or immune system signaling molecule, has been shown to induce the production of interferon-gamma and tumor necrosis factor-alpha (TNF-alpha), two other cytokines that stimulate immune system cells to attack and destroy cancerous cells. Synthetic polyamine analogs are another class of signaling agents that interfere with normal cellular function and induce programmed cell death. Bryostatin-1 is yet another antitumor agent that induces programmed cell death, in this case by interfering with the cellular processing of cancer-causing genes.

Numerous other experimental agents are undergoing intense laboratory and clinical investigation. With time, the most effective of these will expand the armamentarium used to combat NHL in people with HIV, in the hope of extending and enhancing the lives of those who are battling this serious illness.

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Bob Huff

Paying for Life

THE ISSUES BEHIND DRUG PRICING

Most people today appreciate the value of antiretroviral therapy, if not its price. This is because the price of expensive anti-HIV medications in the U.S. is largely, and thankfully, invisible. Although uninsured or underinsured people with HIV may have to pay for their drugs out of pocket, the cost of pharmaceuticals for most HIV positive Americans is borne by private insurance or by the government through Medicaid or a state AIDS Drug Assistance Program (ADAP). Copayments collected by the pharmacy—which can be a significant burden—are as close as many people get to the byzantine world of prescription drug pricing.

The happy fact is that thousands of people are alive today because of better medications and the generous access that came about during the strong economy of the 1990s. But with Congress feeling less charitable these days, there are disturbing signs of trouble ahead. Increasingly, it seems that if the political will to pay the price of quality health care does not soon find a powerful voice, the combination of shrinking funding and runaway drug costs could put the health of large numbers of people in this country who depend on life-giving medication at risk. The implications for those with HIV are considerable, since drugs are generally the biggest factor in the cost of HIV health care.

The Increasing Cost of Health Care

The U.S. is one of the only wealthy nations without government limits on the price of prescription drugs, and American health-care costs continue to spiral upward, with pharmaceuticals leading the way. Even though most consumers do not bear the cost of their drugs directly, rising prices affect the cost and quality of health care for nearly everyone in the U.S. by way of increased insurance premiums, larger copayment amounts, and growing limits to state-funded programs such as ADAP. As state governments explore ways to control prices, the powerful pharmaceutical industry has countered with its own tactics to preserve drug companies' freedom to set prices without such restraint.

Soaring health-care costs are partly due to escalating drug prices, but are also influenced by the increased consumption of expensive drugs. After restrictions on direct-to-consumer (DTC) drug advertising were relaxed in 1997, prescriptions for advertised medications began to climb as Americans started demanding treatments they saw in the media. As DTC ad spending rose from $1.1 billion in 1997 to $3 billion in 2001, drug prices rose, the pharmaceutical industry grew, and profits expanded significantly. Meanwhile, government entitlement programs dug deeper to pay for drugs, and private insurance premiums became all but unaffordable for anyone without a well-paying, full-time job. In today's troubled economy, with unemployment rising and many small businesses unable to meet the burden of high premiums, one in four Americans lacks health insurance, and their ranks are growing.

Over the past couple of years state governments have begun to fight runaway drug costs by attacking the problem on two fronts. First, there has been an attempt to limit utilization by requiring doctors to obtain prior authorization for expensive drugs that are not included on an approved formulary list. In practice, the hurdle of seeking approval to prescribe certain drugs means that doctors often select a similar, cheaper substitute. Problems arise when patients are told at the pharmacy that their prescription cannot be filled because it is not approved; many are likely to give up and go untreated. This sort of manipulation—along with cracking down on waste and fraud—may produce some savings, but in reality, people with complex chronic diseases risk having their care compromised by these restrictive rules. Certainly any effort to cut utilization of anti-HIV medications would be met with anger and outrage.

On the price front, some states such as Michigan and Maine have been trying to win discounts from pharmaceutical manufacturers in exchange for adding their drugs to the state's approved Medicaid formulary, thus removing the barrier to prescribing. This is a powerful stick to wield, since drug companies are loath to yield any market share to their competitors. The pharmaceutical industry deplores this strategy and is fighting back with court challenges, sophisticated public relations campaigns, and drug giveaways via company-run disease management programs aimed at Medicaid patients. In Florida, the pharmaceutical lobby prevailed on Governor Jeb Bush to water down state formulary restrictions by allowing drug companies to offer case management of "high utilizers" instead of discounts. But the industry recently suffered a setback when the Supreme Count voted to allow a program to go forward in Maine that seeks additional rebates for state Medicaid drug purchases. Companies that don't comply will see their products parked on a prior authorization list.

Why Is Price a Problem?

High prices can become a problem when a drug is available only as a brand-name product from a single manufacturer, as is the case with antiretrovirals in the U.S. Every approved anti-HIV drug sold in this country is

Drug Pricing Key Terms

340B (PHS) Price
The maximum price that manufacturers can charge covered entities participating in the Public Health Service's 340B drug discount program.

Acquisition Cost (AC)
The net cost of a drug paid by a pharmacy. It varies with the size of container purchased (e.g., ten bottles of 100 tablets typically costs more than one bottle of 1,000 tablets) and the source of purchase (manufacturer or wholesaler).

AIDS Drug Assistance Program (ADAP)
A federal program established in 1987 to provide anti-HIV and related medications to low-income Americans.

Average Manufacturer Price (AMP)
The average price paid to a manufacturer by wholesalers for drugs distributed to retail pharmacies. The Congressional Budget Office estimates AMP to be about 20% below AWP for more than 200 drugs frequently purchased by Medicaid recipients.

Average Sales Price (ASP)
A new system created by federal and state governments to ensure more accurate price reporting. ASP is the weighted average of all nonfederal sales to wholesalers and is the net of chargebacks, discounts, rebates, and other benefits tied to the purchase of the drug product, whether it is paid to the wholesaler or the retailer.

Average Wholesale Price (AWP)
A national average of list prices charged by wholesalers to pharmacies. AWP is sometimes referred to as a "sticker price" because it is not the actual price that larger purchasers normally pay, which is often considerably lower. AWP information is publicly available.

Best Price
The lowest price paid to a manufacturer for a brand name drug, taking

into account rebates, chargebacks, discounts, or other pricing adjustments, excluding nominal prices. Best price data are not publicly available.

Covered Entities
Facilities and programs eligible to purchase discounted drugs through the Public Health Service's 340B drug discount program. Covered entities include state ADAPs and hospitals owned by state and local governments.

Dispensing Fee
The charge for the professional services provided by the pharmacist when dispensing a prescription, which may include overhead expenses and profit.

Federal Supply Schedule (FSS)
The collection of multiple-award contracts used by federal agencies, U.S. territories, Indian tribes, and others to purchase supplies and services from outside vendors. FSS prices for the pharmaceutical schedule are based on the prices that manufacturers charge their "most-favored" nonfederal customers, which may not be the lowest prices on the market. FSS prices are publicly available.

Medicaid (known as Medi-Cal in California)
A program using state and federal funds to reimburse providers that offer medical care to low-income Americans who cannot afford health insurance. Medicaid serves 55% of people with AIDS and 90% of children with HIV/AIDS nationally. Medi-Cal is the largest payer of health-care services for people with HIV/AIDS in California.

Medicare
A federally administered system of health insurance available to people aged 65 and over and some others with disabilities.

Non-Federal Average Manufacturer Price (Non-FAMP)
The average price paid to a manufacturer by wholesalers for drugs

still under patent protection. A patent guarantees the holder an exclusive right to market the protected product without competition for a period of at least 20 years. After the patent protection period has expired, other manufacturers are free to produce a nonbranded, generic version of the product and sell it at a fraction of the price of the branded drug. In the pharmaceutical business, a good example is fluoxetine (Prozac), which sold for $2.50 per pill until its patent ended in 2001 and a generic manufacturer brought its version to market for only $0.25 apiece.

The first anti-HIV drug expected to lose U.S. patent protection is AZT (zidovudine, Retrovir), which could become available generically in the U.S. sometime after 2005. Since most people who use AZT these days take it with 3TC (lamivudine, Epivir) in the form of Combivir, generic AZT is unlikely to have much impact in this country. Several generic antiretrovirals are now produced in other parts of the world, helping to make treatment a possibility for the millions of people in countries without access to expensive branded medications. But generics have not yet directly affected the pricing situation for anti-HIV drugs in the U.S.

Historically, when a generic equivalent enters the market, the profit potential of the original branded drug virtually vanishes. The price of the generic is set at some margin above the cost of materials, manufacturing, and distribution, and the maker of the branded drug must lower its price or give up the market. The prices of generic equivalents can be set so low because their makers typically invest little or nothing in drug discovery, clinical research, and marketing.

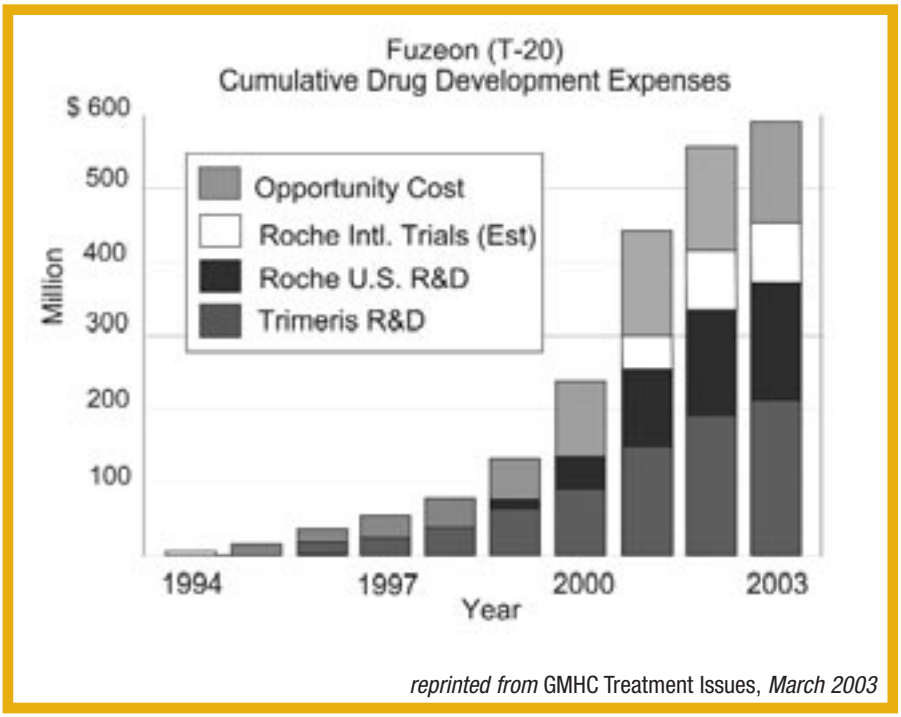
Major pharmaceutical manufacturers argue that the significant cost of bringing new drugs to market justifies the high prices they charge. Furthermore, since the window of premium pricing is limited by a product's patent life—a good portion of which is used up during the approval process—all of a drug's research and development costs must be recouped within a relatively short period of time. Critics of exorbitant drug costs point out that the pharmaceutical industry, despite its complaints, remains one of the most profitable sectors of the economy, and that development costs are overstated and are often subsidized by the government. Drug pricing, critics say, is driven by greed and by the monopoly protection allowed by patents. The true cost of high drug prices, they say, is measured in lives lost.

But the generic price advantage may not be a reliable solution to the current drug cost crunch. Consolidations among generic manufacturers are reducing competition, and generic manufacturers—seeing the gap between their prices and those of branded products as a wasted opportunity—recently have begun raising the sticker price on their knockoffs, thus further intensifying the squeeze on state and federal drug budgets.

Have I Got a Deal for You!

One of the hardest things to understand about pharmaceutical pricing is that not everyone pays the same price. And the prices for different payers are often secret. The only official price released by a pharmaceutical company is called the wholesale acquisition cost (WAC), which is the list price that industry middlemen are supposed to pay the pharmaceutical maker. The wholesaler, in turn, distributes the drug to pharmacies for retail sale.

A more widely quoted price for drugs is the average wholesale price (AWP), which is an average of list prices quoted by wholesalers to pharmacies. But because of an arcane system of discounts, rebates, and chargebacks, almost no one pays the "official" price. The acquisition cost (AC) is the actual amount a pharmacy pays for its drug inventory. This cost varies depending on the quantity purchased, as well as on the rebates and discounts available to the pharmacist. Large buyers can obtain significant discounts: you can almost be sure that a drugstore chain like Duane Reade is paying less for pharmaceuticals than an independent



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neighborhood drugstore, although this may not translate into lower prices for consumers. A recent survey of 155 New York City pharmacies found the highest prices at the biggest chain stores, which charged, on average, 8% more than mom-and-pop stores. Shockingly, the report also found that chain stores in the poorest neighborhoods charged prices well above the citywide average, meaning that those who can least afford high drug prices in New York are paying the most.

After acquiring a drug, the pharmacy then resells it to consumers with or without an additional markup, plus something called a dispensing fee added on. The dispensing fee is a charge for the professional services of the pharmacist, plus an additional percentage of the drug's cost to cover overhead and profit. Each of these steps may be regulated or fixed by prior agreement. For example, some Medicaid programs may limit the dispensing fees charged by retail pharmacists.

A complex system of rebates for government purchasers has been negotiated to help control drug costs. The size of the rebates paid by the manufacturer varies depending on who pays the bill when a prescription is filled. The average manufacturer price (AMP) is a government-calculated average of prices for a drug actually paid by nongovernment purchasers. Although not officially disclosed, the AMP is estimated to run about 20% below the AWP. Government programs use the AMP as a baseline to calculate rebates, with the Medicaid rebate statutorily (by law) set at 15.1% of the AMP.

For programs that distribute drugs directly to their clients, the Public Health Service has established a discount plan that guarantees something called the 340B price, which at minimum matches the Medicaid 15.1% price break, although participating programs are free to negotiate better discounts. Such federally approved 340B participants include hemophilia treatment centers, family planning clinics, and ADAPs that run their own distribution systems. Most big ADAPs, however, distribute their drugs through pharmacies and are organized as reimbursement programs. This means that, for each covered drug dispensed, the state reimburses the pharmacy the AWP minus any special discounts, plus the dispensing fee. The state then collects its negotiated rebate directly from the manufacturer.

distributed to nonfederal purchasers. The Big 4 are entitled to discounts on brand-name drugs of at least 24% off of non-FAMP. (The Big 4 are the four largest purchasers of pharmaceuticals within the federal government: the Veterans Administration, the Department of Defence, the Public Health Service, and the Coast Guard.) Non-FAMP is not publicly available.

Opportunity Cost
The difference between the return on a given investment and the return on foregone alternatives.

Pharmacy Discount Price
The price paid to the pharmacy by a program (e.g., ADAP, Medicaid) for drugs. Brand-name drug prices are typically paid relative to AWP (for example, AWP minus 10%). The price covers the pharmacy's payment to the wholesaler, operating costs, and profit.

R&D
Research and development.

Unit Rebate Amount (URA)
The rebate amount paid by a manufacturer to ADAP and Medicaid for each unit (e.g., capsule) of a drug. Information on URA is not publicly available.

VA National Contract Price
The price the Veterans Administration has obtained though competitive bids from manufacturers for select drugs in exchange for their inclusion on the VA formulary. Because the VA is entitled to something called the Federal Ceiling Price (FCP), VA national contract prices are often the lowest in the nation. These prices are publicly available.

Wholesale Acquisition Cost (WAC)
The price paid by a wholesaler for drugs purchased from the wholesaler's supplier, typically the manufacturer of the drug. WAC is the price manufacturers release publicly, and is sometimes called the "list price." Publicly disclosed or listed WAC amounts may not reflect all available discounts.

The Best Is Not Good Enough

The "best price" is a proprietary federal determination of the lowest price paid by a manufacturer's best customers after rebates and discounts have been applied. Best price is one of the factors used to calculate the rebates owed to state Medicaid programs. Yet certain customers getting some of the best deals are left out of the best price equation.

For example, some government agencies that purchase drugs directly from manufacturers may enjoy extra discounts, which, if included, would bring the average best price down. Another large government purchaser, the Veterans Administration, negotiates a price that is published as the Federal Supply Schedule (FSS) price. The FSS price is based on what drug makers charge their "most favored" nonfederal customers—which, again, may not be the lowest price on the market if, for example, Wal-Mart negotiates a special deal on atorvastatin (Lipitor). Both the 340B and the FSS prices are excluded from the best price calculation.

So what is the price of any particular drug? It depends on who's paying and who's asking, since neither the government nor the manufacturers disclose that information. For example, take tenofovir DF (Viread), produced by Gilead Sciences. The published WAC is $360 for a 30-day supply; an online pharmacy advertises it for $435; and a state ADAP program may pay $380. As a point of comparison, Gilead has offered tenofovir to antiretroviral treatment programs in developing countries at $39 per month, roughly the company's cost of manufacturing.

Other Factors Affecting Price

Another aspect of a drug's price is less often discussed: what is it worth to the individual? The advent of the eBay online auction model has rationalized the pricing of all kinds of products and services by offering them to a wide market and letting individual buyers decide what they are willing to pay. But for products that are necessary to preserve human health and life, society has decided that some unregulated markets are unacceptable. Governments and large private health systems such as Kaiser Permanente use their clout as huge purchasers of pharmaceuticals to demand lower prices, and the states are attempting to control prices with rules, legislation, and group bargaining power. Yet there are ways around these pressures. Statutory discounts can be thwarted by raising the base price until the discounted price matches what the company would prefer the customer to pay. Where price increases for existing products are capped, a company may introduce a reformulation of an old drug at a new benchmark price.

Some prices are set where they are because that is how much other, similar products cost. For example, there are probably few similarities between the operating costs of cable and satellite television, yet remarkably both services are priced the same. And why does high-speed Internet access via DSL cost the same as access via cable? Well, providers reason, if that is what people are willing to pay, then why should they be charged less? When protease inhibitors (PIs) first entered

Risky Business:
THE CASE OF T-20

Although the pharmaceutical industry has remained profitable despite the tough economic climate of the past few years, the costs and risks associated with identifying and shepherding a new anti-HIV drug to market are considerable.

The latest antiretroviral approved for sale in the U.S. has brought the issue of drug pricing to center stage. T-20 (enfuvirtide, Fuzeon), discovered by Trimeris and developed and marketed in partnership with Hoffmann-La Roche, entered the market in March 2003 as the most expensive anti-HIV drug ever. With an announced wholesale acquisition cost (WAC) of $20,000 per year, the cash-and-carry price at the pharmacy reaches $26,400 annually, or $2,200 per month.

The development of T-20, the first in a new class of entry inhibitor drugs, began over ten years ago, and it took five years and $50 million to demonstrate it was a viable therapy in humans. Finally, after ten years and $600 million invested, the drug made it to market, but it remains unclear how accepting consumers will be of a drug that must be injected twice daily and causes injection-site nodules or irritation in most people who use it. Presumably, the population for whom T-20 is intended—those who have developed resistance to most other available antiretrovirals and have run out of therapeutic options—will be willing to put up with the discomfort and inconvenience for a chance at survival. But will that willingness extend to government programs that pay for life-saving medications for people with HIV, especially in parlous economic times? The risk for Trimeris and Roche is that after all the money and time invested, only a limited number of people will be able to benefit from T-20. The risk for those with multidrug-resistant virus is that a useful therapy will remain out of reach because the price is simply too high. *–B.H.*

the market in December 1995, they established a new benchmark for the price of HIV/AIDS medication, and the industry hasn't looked back since. This seems to be a lesson the generic drug industry is now putting into practice.

Price also reflects the value offered by a drug. For hepatitis C virus (HCV), for example, the price of a yearlong course of treatment includes the chance that one's infection may be permanently cleared. Currently, the newest and best HCV therapies can run upwards of $35,000 per year. But with HIV, there is no cure, and the need for therapy lasts a lifetime. The average yearly cost of anti-HIV therapy in the U.S. currently runs between $10,000 and $15,000. The price of drugs may also be weighed against the cost of hospitalization and care for untreated HIV, and thereby judged to be a bargain. A new, pricier drug may have fewer side effects and require less medical management than its cheaper predecessors. In the big picture, it is a money-saver (though in the short term it is still a drain on state budgets). Some economists have calculated the value of drug therapy in relation to lost productivity due to early death from AIDS. Few people who lived through the bad old days before PIs would say that the latest antiretrovirals aren't worth the cost.

Pressure Politics

But we may be entering an era in which political leadership demands more reasonable cost controls. There are powerful forces influencing political leaders today. On the one hand, health-care costs are soaring out of control and the political will to pay for them may be diminishing. On the other hand, the biggest contributor to rising costs—the pharmaceutical industry—is represented by an extensive and pervasive lobby that makes significant contributions to influential members of Congress and the Administration. In the ongoing struggle between those who wish to downsize government spending and the big donors, it looks increasingly as if something has to give.

The major battlefield is turning out to be the question of whether Medicare, the medical insurance program for seniors (and some people with disabilities), will be able to offer a prescription drug plan. Currently this government program does not cover prescription drugs. Unless they have supplemental insurance, people who rely on Medicare pay for their medications out of pocket—which means that those who can least afford it often pay higher prices than almost anyone else.

The plight of seniors has received high-profile coverage on the nightly news, complete with footage of old folk boarding buses bound for discount pharmacies in Canada. Internet sites that fill prescriptions at the more affordable Canadian prices have come under attack as some major pharmaceutical companies have refused to sell their products to Canadian pharmacies that ship drugs back to the U.S. It is not clear whether there is a significant benefit to shopping in Canada for people with HIV: the listed Canadian pharmacy price for a month's supply of 3TC is US$230, compared with Walgreens' U.S. price of $295.

Despite the pain inflicted on those least able to pay, large drug companies are fighting against a Medicare drug benefit with all of their political muscle, mainly because they fear the leverage the government would gain if it

ADAP IN CRISIS

The AIDS Drug Assistance Program (ADAP), established in 1987 to provide anti-HIV and related medications to low-income Americans, is a cornerstone of U.S. treatment efforts. Nationally (including U.S. territories), ADAPs serve about 140,000 people who could not otherwise afford these critical treatments. While paying for ADAP is primarily a responsibility of the federal government, Congress and the president have failed in recent years to provide adequate funds to assure unlimited access to the program. In fiscal year (FY) 2003, Congress appropriated $719 million for ADAP, an increase of $80 million over 2002. However, this increase fell $80 million short of what was needed. In FY 2004, President Bush has proposed spending $739 million on ADAP, but this amount is a massive $260 million below the $999 million needed to guarantee access to treatment for those who rely on ADAP.

To guarantee access to ADAP and make up for the lack of sufficient federal funding, many states have allocated their own money to the program. But in an era of severe budget deficits, most states are finding it difficult to keep up with growing drug costs and ADAP enrollments. In response, some states are creating waiting lists to enter the program. Others, including Texas, are tightening income requirements to cover only some of the people who were previously eligible. Still other states are making important drugs unavailable. California's governor recently proposed that ADAP clients—including those unable to work—make copayments to participate in the program, but advocacy efforts appear to have stymied this development.

The San Francisco AIDS Foundation (SFAF) is working with many partners to assure that ADAP is fully funded, both at the national level and in California. To join in efforts to maintain this crucial program, please contact the SFAF Policy Department at 415-487-3080 or dvangord@sfaf.org. *–Dana Van Gorder*

were able to negotiate prices for seniors, the largest sector of drug consumers. As a paragraph from Pfizer's 2002 annual report cautions investors:

"In the U.S., many pharmaceutical products are subject to increasing pricing pressures, which could be significantly impacted by the outcome of the current national debate over Medicare reform. If the Medicare program provided outpatient pharmaceutical coverage for its beneficiaries, the federal government, through its enormous purchasing power under the program, could demand discounts from pharmaceutical companies that may implicitly create price controls on prescription drugs."

While such behavior could be attributed to greed, a more charitable view is that pharmaceutical companies are driven by insecurity about unknown risks. Chief among these risks is that revenue streams could dry up if outside forces unexpectedly impinge on prices. Yet the next line in Pfizer's report recognizes that change may present opportunity: "On the other hand, a Medicare drug reimbursement provision may increase the volume of pharmaceutical drug purchases, offsetting at least in part these potential price discounts."

[Ed. note: both the House of Representatives and the Senate have recently passed legislation that would provide a limited prescription drug benefit through Medicare. While the two plans are different, neither is comprehensive and each would require significant out-of-pocket expenditures for Medicare recipients by way of premiums, copayments, and coverage gaps.]

Virtually everyone agrees that mounting drug costs are causing distress, but no one has yet developed a political accommodation that can ensure access to needed medications for all, while continuing to support research into newer and better drugs for those who will need them tomorrow. Meanwhile, budgets continue to strain as more and more people come to depend on life-giving pharmaceuticals whose prices rise with no end in sight.

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

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HIV ADVOCACY • GET INVOLVED •

AIDS Treatment Activists Coalition (ATAC)

ATAC is a dynamic new coalition of people working together to improve HIV research and treatment access in the U.S.

ATAC encourages greater, more effective involvement of all people with HIV in decisions—made by the pharmaceutical industry, government, and others—that affect their lives. To bolster the ranks of treatment activists, the coalition is committed to identifying, mentoring, and empowering new activists in all communities affected by the epidemic.

ATAC Contact Information

Web site
www.atac-usa.org

E-mail
info@atac-usa.org

JOIN THE E-MAIL LISTSERV—
send a message including your real name and a description of your AIDS treatment activism to:
info@atac-usa.org

We're Updating Our Database!

Please send your e-mail address to us at *beta@sfaf.org*

pangaea
GLOBAL AIDS FOUNDATION

The Pangaea Global AIDS Foundation is dedicated to battling the impact of HIV at the international level, particularly in developing nations.
Find out more about Pangaea at **www.pgaf.org** or call **415-581-7000.**

Monitoring Tests for People with HIV

Liz Highleyman

A wide variety of monitoring tests are available to help gauge HIV disease progression and the state of overall health. HIV viral load tests provide a picture of viral activity, while CD4 cell counts shed light on the status of the immune system and can help physicians predict—and therefore prevent—the development of opportunistic illnesses (OIs). These tests can help guide treatment decisions and indicate whether treatment is working. Viral load tests and CD4 cell counts offer a more accurate representation of HIV activity and disease progression than older, indirect surrogate markers—such as beta-2 microglobulin and neopterin—that are no longer commonly used.

In addition, general tests such as the complete blood count, the blood chemistry panel, and blood sugar and lipid (fat) tests can help keep track of side effects such as low blood cell counts, liver toxicity, and elevated triglyceride and cholesterol levels. Other tests, such as genotypic and phenotypic resistance assays and therapeutic drug monitoring, can help optimize anti-HIV therapy.

Almost all the laboratory tests described in this article require a blood sample; fortunately, a single sample often can be used for several different assays. Typically, a person with HIV or his or her physician will receive a report that combines several test results, along with normal or "reference" ranges. In many cases, a person should receive initial tests as soon as possible after an HIV diagnosis to establish a baseline against which future tests may be compared. In general, most monitoring tests should be performed every 3–6 months or so. Results obtained by different laboratories and different test methods can vary greatly, and results may even vary from day to day at the same lab. Tests should preferably be done at the same lab using the same procedure each time, to allow for more accurate comparisons.

Many factors—such as time of day, recent vaccinations, and concurrent infections such as the flu—may influence test results. A test that returns an unexplained or unexpected result should be repeated. A single abnormal lab result is not always cause for concern; upward and downward trends over time are usually more important. (The normal lab values given below and in the chart on page 38 represent typical reference ranges; values may vary considerably between laboratories.)

Complete Blood Count

Whole blood is made up of various types of cells suspended in a liquid called plasma. The complete blood count (CBC) is an inventory of the different cellular components of the blood: red blood cells, white blood cells, and platelets. This test is important because people with HIV may have low blood cell counts (cytopenias) due to chronic HIV infection or as a side effect of medications, particularly drugs that damage the bone marrow, where all blood cells are produced. Blood cell counts are typically reported as the number of cells in a cubic millimeter of blood (cells/mm^3) or as a percentage of all blood cells. Most experts recommend that people with HIV should receive a CBC about every six months, and more often if they are experiencing symptoms or taking drugs associated with low blood cell counts.

Red Blood Cells

Red blood cells (erythrocytes) carry oxygen from the lungs to the body's cells, bound to a molecule called hemoglobin. Anemia is a condition characterized by a reduction in the number of red blood cells, often leaving a person fatigued, weak, and short of breath. Anemia is common in HIV positive people. HIV itself and various OIs such as *Mycobacterium avium* complex (MAC) can affect red blood cells and their oxygen-carrying capacity. In addition, drugs such as AZT (zidovudine, Retrovir) may lead to low red blood cell counts due to bone marrow suppression, while other medications such as ribavirin (used to treat hepatitis C) can directly destroy red blood cells (hemolysis). Several tests are used to help diagnose various types of anemia.

Red Blood Cell Count (RBC): the total number of red blood cells in a quantity of blood. Normal ranges are 4.5–6.0 million cells/mm^3 for men and 4.0–5.5 million cells/mm^3 for women. (Women typically have lower counts than men due to the loss of blood through menstruation.)

Hematocrit (HCT): the proportion of red blood cells as a percentage of total blood volume. A normal hematocrit is 40–55% for men and 35–45% for women.

Hemoglobin (HGB): the number of grams of hemoglobin in a deciliter of blood (g/dL). Normal levels in healthy adults are 14–18 g/dL for men and 12–16 g/dL for women. As a rough guideline, hemoglobin should be about one-third the hematocrit.

Mean Corpuscular Hemoglobin (MCH) and MCH Concentration (MCHC): the amount or concentration, respectively, of hemoglobin in an average red blood cell.

Mean Corpuscular Volume (MCV): the average size, or volume, of individual red blood cells. Conditions such as iron deficiency can lead to smaller than normal red blood cells, while certain vitamin deficiencies and some drugs (including nucleoside reverse transcriptase inhibitors [NRTIs]) can produce larger than normal cells.

Red Blood Cell Distribution Width (RDW): a measure of the size and uniformity of red blood cells.

White Blood Cells

White blood cells (leukocytes) carry out the body's immune responses. The CBC looks at numbers of various different types of white blood cells.

White Blood Cell Count (WBC): the total number of white blood cells in a quantity of blood. A healthy adult normally has 4,000–11,000 white blood cells/mm^3. A WBC increase often indicates that a person is actively fighting an infection or has recently received a vaccine. Decreased WBC (leukopenia) can leave a person vulnerable to various pathogens and cancers.

Differential: a report of the proportions of different types of white blood cells as a percentage of the total number of white cells; these percentages may be multiplied by the WBC to obtain absolute counts. People with HIV should be especially concerned with neutrophil and lymphocyte levels, in particular CD4 and CD8 cell counts (discussed below).

Neutrophils: a type of cell that fights bacterial infections. Neutrophils normally make up about 50–70% of all white blood cells. Various anti-HIV drugs (especially AZT), OI medications (including ganciclovir [Cytovene], used to treat cytomegalovirus, or CMV), and cancer chemotherapies that suppress the bone marrow may lead to low neutrophil levels (neutropenia). The risk of bacterial infection increases when the absolute neutrophil count falls below about 500–750 cells/mm^3.

Lymphocytes: there are two main types of lymphocytes. B cells produce antibodies that fight foreign invaders in the body, while T cells target infected or cancerous cells and help coordinate the overall immune response. A normal lymphocyte count is about 20–40% of all white blood cells. The typical differential does not include specific subsets of T cells, but because CD4 and CD8 cell counts are important to people with HIV, they are measured separately (discussed below).

Monocytes: a type of cell that fights pathogens by engulfing and destroying them. Monocytes circulate in the blood for about 24 hours; when they leave the bloodstream and migrate into the tissues, they mature into macrophages. Monocytes and macrophages normally account for 2–10% of all white blood cells.

Eosinophils: cells that play a role in defense against parasites and in allergic reactions. They normally make up 0–6% of all white blood cells.

Basophils: another type of cell involved in allergic reactions, in particular the release of histamine. They normally account for 1% or less of all white blood cells.

Platelets

Platelets (thrombocytes) are necessary for blood clotting. A normal platelet count is about 130,000–440,000 cells/mm^3. Low platelet counts (thrombocytopenia)—which can lead to easy bruising and excessive bleeding—may be caused by certain drugs, autoimmune reactions, accelerated destruction by the spleen, or HIV disease itself.

CD4 and CD8 Cell Tests

CD4 Cell Count

As noted above, T cells are types of lymphocytes that help the body get rid of infected or cancerous cells and help coordinate the immune response. CD4 cells (also known as T4 or T-helper cells) carry the CD4 receptor molecule on their surface and coordinate the cell-mediated immune response. Most CD4 cells reside in the lymph nodes, and various factors can cause them to enter or leave the bloodstream. A normal CD4 cell count in a healthy adult is about 600–1,200 cells/mm^3; it tends to be somewhat higher in women than in men, and considerably higher in young children. CD4 cell counts often fluctuate due to factors including time of day (levels are usually higher in the morning), fatigue, stress, vaccinations, infections such the flu, and monthly menstrual cycles in women.

HIV primarily targets CD4 cells. As HIV disease progresses, CD4 cell counts decline, typically by about 30–100 cells/mm^3 per year (depending on viral load), leaving a person increasingly vulnerable to infections and cancers. People with CD4 cell counts above 500 cells/mm^3 generally have relatively normal immune function and are at low risk for OIs.

When the CD4 cell count drops below 200 cells/mm^3, an individual is prone to infections such as *Pneumocystis carinii* pneumonia (PCP). The risk is even greater when the CD4 cell count declines further; people with fewer than 100 cells/mm^3 may contract OIs such as toxoplasmosis and cryptosporidiosis, while those with fewer than 50–75 cells/mm^3 are at risk for MAC and CMV. A CD4 cell count below 200 cells/mm^3 or a CD4 percentage below 14% signals a diagnosis of AIDS.

The CD4 cell count is a valuable tool for gauging HIV disease progression. Along with viral load, it provides information about when anti-HIV therapy is indicated and how well it is working; effective treatment can halt HIV replication and restore CD4 cell levels. Current U.S. HIV treatment guidelines recommend that people should consider starting anti-HIV therapy when their CD4 cell count falls below 350 cells/mm^3. In 2001 this level was reduced from 500 cells/mm^3 after research showed little benefit to starting treatment in asymptomatic people with 350–500 cells/mm^3, especially given the adverse effects, inconvenience, and cost of therapy. Studies are underway to assess the value of treatment in people with 200–350 cells/mm^3.

Many people who have started combination anti-HIV therapy have seen dramatic increases in their CD4 cell counts and have been able to safely stop OI prophylaxis (preventive treatment). However, the CD4 cell count tends to eventually drop back to its previous lowest level—known as the nadir—if anti-HIV therapy is discontinued. Importantly, CD4 cell numbers do not tell the whole story: how well the cells function and what pathogens they target are also important. (Tests of T cell activation and proliferation are available as research tools, but are not widely used in clinical practice.)

Most experts recommend that the CD4 cell count should be measured when HIV is diagnosed, then every 3–6 months or so—closer to three months if the count is low or falling or a person is starting or changing treatment, and closer to six months if the count is high or has been stable for several months. An individual CD4 cell measurement is not as informative as downward or upward trends over time; any large or unexpected change should be confirmed with a repeat test.

CD8 Cell Count

Two types of T cells carry the CD8 surface molecule: T-suppressor cells, which inhibit immune responses, and killer T cells (also known as cytotoxic T lymphocytes, or CTLs), which target and kill infected or cancerous cells. A normal CD8 cell count is about 200–1,000 cells/mm^3. As with CD4 cells, a variety of factors can cause CD8 cell counts to fluctuate. CD8 cell counts typically rise over time in people with HIV, but (unlike CD4 cells) CD8 cell numbers do not independently predict disease progression, and their relation to immune status is not well understood.

CD4 and CD8 Cell Percentage

Because absolute CD4 and CD8 cell counts are so variable, some physicians prefer to look at CD4 or CD8 cell percentages—that is, the proportion of all lymphocytes that are CD4 or CD8 cells. Percentages are usually more stable over time than absolute counts. A normal CD4 cell percentage in a healthy person is about 30–60%, while a normal CD8 cell percentage is 15–40%.

CD4/CD8 Cell Ratio

The CD4/CD8 cell ratio will also be reported. This is calculated by dividing the CD4 cell count by the CD8 cell count. A normal CD4/CD8 cell ratio is about 0.9–3.0 or higher—that is, there are at least 1–3 CD4 cells for every CD8 cell. In people with HIV this ratio may be much lower, with many more CD8 cells than CD4 cells.

Blood Chemistry Tests

The blood chemistry, or chem panel, measures many important substances in the blood. Although the chem panel does not directly measure HIV disease progression, it can help indicate how well various organs are functioning and provide valuable information about drug side effects. A chem panel should be done at least every six months, and more often in people who are experiencing symptoms or taking drugs that can adversely affect blood values. As noted previously, different laboratories have different reference ranges for what they consider normal values.

Electrolytes

Electrolytes are positively or negatively charged molecules (ions) that play important roles in cellular activity and heart and nerve function. Normally electrolyte levels are regulated

by the kidneys, and any excess is excreted in the urine. Most healthy people can get all the electrolytes and other minerals they need by eating a balanced diet. Electrolyte imbalances may signal malnutrition, kidney problems, or dehydration (which may be caused by prolonged vomiting or diarrhea). Such imbalances are not uncommon in people with acute or chronic illnesses.

Bicarbonate: a form of carbon dioxide (CO_2) in the blood. Bicarbonate acts as a buffer to help maintain the body's acid-base balance (pH). A normal bicarbonate level is about 22–33 millimoles per liter (mmol/L). A high level might indicate an "anion gap," which may signify high lactate levels or lactic acidosis (an adverse effect associated with NRTIs).

Calcium: a major component of bones and teeth, calcium is also required for proper nerve and muscle function. A normal total serum calcium level is 8.5–10.5 milligrams/deciliter (mg/dL).

Chloride: sodium and chloride are often found together, and both help regulate the body's fluid balance. A normal chloride level is 95–105 mmol/L.

Magnesium: this mineral plays a role in nerve impulse transmission and muscle contractions. A normal range is 1.5–3.0 mg/dL.

Phosphorus: most of the body's phosphorus is located in the bones, but it also plays an important role in maintaining the body's pH balance. A normal level is 2.0–4.5 mg/dL.

Potassium: this mineral also plays a role in nerve impulse transmission and muscle function. A normal level is 3.5–5.0 mmol/L. Abnormal potassium levels may be related to kidney failure or dehydration.

Sodium: this mineral is important in maintaining the body's fluid balance and is involved in transmission of nerve impulses. A normal level is 135–145 mmol/L. Abnormal sodium levels may be due to dehydration, elevated lipid levels, or kidney dysfunction.

Liver Function Tests

Liver function tests, also known as the hepatic panel, are laboratory tests that help measure how well the liver is working. The liver carries out many vital bodily functions; when it is not working properly, levels of various enzymes, proteins, and other substances in the blood may rise or fall. Elevated liver enzyme levels may be a sign of liver damage caused by factors such as viral hepatitis, heavy alcohol consumption, or drug toxicity. Because several anti-HIV medications are known to cause liver damage (hepatotoxicity), people taking antiretroviral therapy should have their liver function monitored regularly, about every two months. This is especially important for people coinfected with the hepatitis B or C viruses.

Alanine transaminase (ALT): formerly called SGPT, ALT is an enzyme normally present in liver cells. When these cells are damaged, ALT is released into the bloodstream. A normal ALT level for adult men is 0–50 International Units per liter (IU/L); levels are somewhat lower in women. While mild elevations are common, an ALT level more than 2.5 times the upper limit of normal (ULN) is cause for concern. Recent research has shown that even moderately elevated ALT or AST levels in people with HIV are associated with a higher risk of death. In general, upward or downward trends in ALT are more informative than a single measurement.

Aspartate transaminase (AST): formerly called SGOT, AST is another liver enzyme that may spill into the blood when liver cells are damaged. AST levels may also be elevated in people with muscle damage. A normal AST level for adult men is 0–45 IU/L.

Bilirubin: bilirubin is a pigment released when red blood cells are broken down. A normal bilirubin level is 0.1–1.5 mg/dL. An elevated level (hyperbilirubinemia) may indicate liver damage, impaired bile flow, or excessive red blood cell destruction. High bilirubin levels can lead to jaundice (yellowing of the skin and whites of the eyes).

Alkaline phosphatase (AP): elevated AP levels may signal obstructed bile flow or bone destruction. A normal level is 35–115 IU/L.

Gamma glutamyl transpeptidase (GGT): high GGT levels may also be a sign of impaired bile flow. A normal level is 30–60 IU/L.

Blood clotting measures: liver dysfunction may lead to impaired blood clotting as platelets are destroyed by an enlarged spleen and the liver is unable to produce adequate amounts of clotting factors. Platelet count (described above) and prothrombin time (PT) are two measures of blood clotting ability. PT is an indication of how long it takes the blood to clot; a normal value is about 10–12 seconds. Laboratories usually report PT in seconds and in terms of international normalized ratio (INR). PT is generally considered prolonged if it is 1.2 times normal or slower (INR greater than 1.2).

Kidney Function Tests

Kidney function tests are important for people with HIV because certain anti-HIV drugs (e.g., tenofovir DF [Viread]) and medications used to treat OIs (e.g., foscarnet [Foscavir] for CMV) may cause kidney damage, especially in those with a history of kidney problems. To assess kidney function, urine is usually analyzed in addition to blood tests. The presence of protein, glucose, or red or white blood cells in the urine may be a sign of kidney damage or some other abnormal condition.

Blood urea nitrogen (BUN): nitrogen is a metabolic waste product that is normally filtered out by the kidneys and excreted in the urine. A normal BUN is 8–20 mg/dL. Elevations may indicate kidney dysfunction or a body fluid imbalance (e.g., dehydration).

Creatinine: this waste product of protein metabolism is also normally excreted by the kidneys. A normal blood creatinine level is 0.6–1.5 mg/dL. Elevated creatinine levels may indicate kidney damage.

MONITORING TEST RESOURCES

Understanding Your Lab Results (ACRIA)
www.criany.org/treatment/treatment_edu_lab_results.html
**the print version, but not the web site, contains a sample lab report*

The Blood Tests You'll Need
www.aidsmeds.com/lessons/StartHere4.htm
**includes a sample lab report*

Blood Work (Project Inform)
www.projinf.org/fs/HIVDiagTest.html

Laboratory Tests for Monitoring HIV-1 Infection
www.hivandhepatitis.com/hiv_and_aids/test/lab1.html

Lab Tests Online
www.labtestsonline.org

Other Blood Tests

Albumin: one of the major blood proteins, albumin helps regulate the body's fluid balance and maintain normal blood volume. It also acts as a carrier protein for many drugs. A normal serum albumin level is 3.0–5.5 grams per deciliter (g/dL). An elevated level may be a sign of dehydration, while a low level may indicate malnutrition, liver disease, or kidney dysfunction. A recent study showed that low serum albumin levels are a strong predictor of disease progression and death in women with HIV.

Amylase: this enzyme is produced by certain digestive organs, especially the pancreas. A normal amylase level is 50–160 IU/L. A high level is often a sign of pancreatitis (inflammation of the pancreas). Some anti-HIV drugs (e.g., ddI [didanosine, Videx]) may cause pancreatitis; people taking such drugs should have their amylase levels checked if they experience unexplained symptoms such as abdominal pain.

Creatine phosphokinase (CPK): this enzyme may be released into the blood when muscles are damaged. A normal level is 20–150 IU/L for men and 10–80 IU/L for women. Elevations may be due to heart muscle damage (such as a heart attack), excessive exercise, or muscle toxicity caused by drugs.

Lactate (or lactic) dehydrogenase (LDH): this enzyme is released from damaged cells. A typical reference range is 100–250 IU/L. Elevated levels may indicate widespread inflammation or cell death (necrosis), for example, due to a heart attack, PCP, or lymphoma (cancer of the lymphoid tissue).

Testosterone: both men and women produce this steroid hormone, and research suggests that levels are often decreased in people with HIV. The generally accepted testosterone range is 200–1,200 micrograms per deciliter (µg/dL) for men and 20–60 µg/dL for women. However, levels vary widely among individuals. Low testosterone levels may lead to loss of libido (sexual drive), fatigue, wasting, and depression.

Sedimentation (sed) rate: this test measures how rapidly red blood cells settle in a test tube. An elevated sed rate may indicate inflammation.

Blood Sugar and Lipid Tests

Over the past several years increased attention has focused on unusual metabolic complications in people with HIV. It is still not definitively known whether these manifestations are related to long-term HIV infection itself, immune recovery, antiretroviral drugs, or a combination of these factors. However, dramatically elevated blood lipid (fat) and glucose (sugar) levels have been correlated with the use of protease inhibitors (PIs). Today, most physicians regularly monitor blood fat and sugar levels in their patients taking anti-HIV therapy, and may recommend antiretroviral regimen changes or lipid-lowering medications if levels get too high.

Glucose: sugar is carried in the blood in the form of glucose, which is broken down by cells to provide energy. A normal glucose level is 65–125 mg/dL. A persistently high glucose level is a sign of diabetes mellitus. It may indicate that the pancreas is not producing enough insulin (a hormone that allows the body to use glucose), or that the body is not responding normally to the insulin produced, a condition known as insulin resistance. Some anti-HIV drugs—particularly PIs—have been associated with insulin resistance and elevated glucose levels. In addition to tests that measure blood glucose at a single point in time, the hemoglobin A1c test can help assess the amount of glucose in the blood over several months.

Triglycerides: after eating, energy that is not needed immediately is converted into triglycerides and transported to fat cells for storage. A normal triglyceride level is about 45–150 mg/dL. Elevated levels (hypertriglyceridemia) are associated with increased risk of cardiovascular disease, especially when accompanied by high cholesterol levels. Extremely high triglyceride levels (greater than about 1,000 mg/dL) can cause pancreatitis. Triglycerides should be measured after fasting for at least eight hours.

Cholesterol: a fatty substance that circulates in the blood, cholesterol is an important component of cell membranes, certain hormones, vitamin D, and bile acids. A healthy total cholesterol level is 120–200 mg/dL. Elevated total cholesterol (hypercholesterolemia) is known to increase the risk of cardiovascular disease, but it is more useful to look at specific types of cholesterol. Low-density lipoproteins (LDL)—so-called "bad" cholesterol—can deposit cholesterol in artery walls, causing atherosclerosis (hardening of the arteries). But high-density lipoproteins (HDL)—so-called "good" cholesterol—help clear cholesterol from the body and may reduce the risk of cardiovascular disease. In some studies, higher HDL levels have been associated with more robust viral load reductions in people taking anti-HIV therapy. The National Cholesterol Education Program recommends that people try to achieve a total cholesterol level below 200 mg/dL, an LDL level below 100 mg/dL, and an HDL level of at least 40 mg/dL.

Tests for Pathogens Other than HIV

Anyone being treated for HIV most likely will have already received antibody tests (usually an enzyme-linked immunosorbent assay, or ELISA, followed by a Western blot test) to confirm the presence of the virus. But providers may recommend additional tests to detect other pathogens.

Serologic (blood serum) tests detect antibodies in the blood that indicate that a person has been exposed to a microorganism and has mounted an immune response. Microbiological tests look for pathogens themselves or their genetic material. While many pathogens can be detected using blood tests, some require other bodily substances—for example, a sputum test for PCP, a stool (fecal matter) test for parasitic infections such as cryptosporidiosis, or a cerebrospinal fluid test (spinal tap) for brain infections such as cryptococcal meningitis.

In most cases, tests for pathogens are performed only if a person is experiencing symptoms of a specific infection. But other tests should be routinely offered to people with HIV. For example, many physicians recommend that people be tested for toxoplasmosis and syphilis when they are first diagnosed with HIV. And, because coinfection is so prevalent, the U.S. Public Health Service and the Infectious Diseases Society of America recommend that all people with HIV should be screened for viral hepatitis. Anyone with significantly elevated liver enzymes should be tested for hepatitis A, B, and C.

HIV Viral Load Tests

Viral load tests measure the amount of HIV RNA (genetic material) in the blood. The presence of RNA indicates that the virus is actively replicating (multiplying). Along with the CD4 cell count, viral load is one of the most valuable measures for predicting HIV disease progression and gauging when anti-HIV treatment is indicated and how well it is working.

Viral load is expressed either as copies of RNA per milliliter of blood (copies/mL) or in terms of logs. A log change is an exponential or 10-fold change. For example, a change from 100 to 1,000 is a 1 log (10-fold) increase, while a change from 1,000,000 to 10,000 is a 2 log (100-fold) decrease. (For a more complete explanation of logs, see the sidebar on page 15.)

If the level of HIV is too low to be measured, viral load is said to be undetectable, or below the limit of quantification. However, undetectable viral load does not mean that HIV has been eradicated; people with undetectable viral load maintain a very low level of virus. Even when HIV is not detectable in the blood, it may be detectable in the semen, female genital secretions, cerebrospinal fluid, tissues, and lymph nodes.

Two types of viral load test are commonly used to measure HIV viral load: Roche's Amplicor HIV-1 Monitor polymerase chain reaction (PCR) assay and Bayer's Quantiplex branched-chain DNA (bDNA) assay. Other viral load tests—Organon Teknika's nucleic acid sequence-based assay (NASBA) and Digene's DNA hybridization test—are newer and less widely used. Only the Amplicor test is currently approved by the U.S. Food and Drug Administration (FDA). While first-generation tests measured viral load down to about 400 copies/mL, the ultrasensitive second-generation tests in widespread clinical use today have a lower limit of detection of about 50 copies/mL; some research tests can measure as few as 5 copies/mL. The older-generation tests are better at measuring high viral loads, while the newer tests more accurately measure low viral loads. (The first-generation PCR test was more sensitive than the first-generation bDNA assay, but the newer versions of both tests are comparable.)

A viral load of 100,000 copies/mL or greater is considered high, while levels below 10,000 copies/mL are considered low. Research has consistently shown that higher viral loads are associated with more rapid HIV disease progression and an increased risk of death. Current U.S. HIV treatment guidelines recommend that people should consider starting treatment if their viral load is above 55,000 copies/mL (revised upward from 10,000 copies/mL in the previous guidelines). Importantly, most studies that have correlated viral load and HIV disease progression have been done in men; more recent research indicates that women may progress to AIDS at lower viral load levels, suggesting that the treatment threshold should perhaps be revised downward for women.

Effective anti-HIV treatment can often reduce viral load to low or undetectable levels. Therapy that does not produce an undetectable viral load is often said to be failing. Another warning sign is viral breakthrough, an increase in viral load following earlier suppression. Inability to achieve an undetectable viral load may mean that a person's HIV is resistant to the drugs being used. Providers often take this as an indication to change or add new

PAP SMEARS

Not all monitoring tests for people with HIV involve blood draws. Research has shown that women and men with HIV are at greater risk of developing genital and anal cancer than HIV negative people. Cervical, penile, and anal cancer are associated with certain strains of the human papillomavirus (HPV), and HPV disease progression appears to be more aggressive in people with HIV.

Pap smears, which are used to detect abnormal cell changes, have dramatically reduced the death rate due to cervical cancer. In a cervical Pap smear, a sample of cells is taken from the cervix (the lower part of the uterus) opening using a wooden spatula or brush and examined under a microscope. Experts recommend that HIV positive women should receive a Pap smear every 6–12 months—closer to six months if previous Pap test results were abnormal, and closer to annually if past tests were consistently normal. In March 2003 the FDA approved a new test to detect high-risk strains of HPV; the Digene HC2 HPV DNA assay is used in conjunction with a Pap smear, using the same sample of cervical cells.

Pap smears are not just for women: experts increasingly recommend that men who have sex with men—whether or not they are HIV positive—receive a yearly anal Pap smear.

If Pap smear results are abnormal, a follow-up test (in which the affected area is examined using a lighted magnifying device) is indicated.

drugs to a person's anti-HIV regimen. However, research suggests that therapy that substantially decreases HIV levels (especially if it reduces them to below 10,000 copies/mL) is likely to be beneficial even if it does not achieve the "gold standard" of undetectability.

Most experts recommend that a viral load test should be done when a person is first diagnosed with HIV to establish a baseline, then every 3–6 months or so. Tests should be done about four weeks after a person starts or changes anti-HIV therapy to monitor whether the new treatment appears to be working. Various factors—such as concurrent infections or recent vaccines—can affect viral load, and blips (brief increases) may occur that do not signal actual HIV disease progression. As with CD4 cell count, an individual measurement is not as useful as downward or upward trends over time.

Treatment Monitoring Tests

As noted above, increasing viral load levels (viral breakthrough) and decreasing CD4 cell counts while a person is taking anti-HIV therapy are indications that adherence is not adequate or that the drugs being used are not effective and may need to be changed. In addition, today there are other tests that can help physicians determine whether current therapy is working or whether a treatment option under consideration is likely to work.

Resistance Testing

HIV can develop drug resistance by mutating in such a way that the virus can continue to replicate despite the drug. (Nonmutated HIV is referred to as "wild-type" virus.) This usually occurs when a drug is not completely effective (due to poor adherence, suboptimal drug levels, or other reasons), allowing HIV to multiply and mutate in the presence of the drug. Also, an increasing number of people are becoming infected with HIV that is already resistant to one or more drugs.

Several studies have shown that use of resistance testing to guide treatment decisions leads to more sustained viral load reductions. The ability to tell which drugs are no longer working provides the opportunity to change a specific drug, rather than tossing out an entire failing regimen. Resistance tests are increasingly being used in clinical practice, but they are not yet standardized and should be interpreted by an experienced physician. The tests work best when a person has a viral load of at least 1,000 copies/mL and is currently still on a failing anti-HIV drug regimen. Three types of tests are used to measure drug resistance. (For more information on resistance testing, see "Salvage Therapy," *BETA*, Winter 2003.)

Genotypic tests: these tests examine the genetic sequence of HIV's reverse transcriptase and/or protease enzymes to look for mutations that are known to be associated with resistance to particular drugs. For example, the K103N mutation

Common Monitoring Tests for People with HIV

Blood Cell Tests

Test	Normal Range
Red blood cell count (RBC)	Men: 4.5–6.0 million cells/mm^3 Women: 4.0–5.5 million cells/mm^3
Hematocrit (HCT)	Men: 40–55% Women: 35–45%
Hemoglobin (HGB)	Men: 14–18 g/dL Women: 12–16 g/dL
Mean corpuscular hemoglobin (MCH)	27–33 picograms/ red blood cell
MCH concentration (MCHC)	32–36%
Mean corpuscular volume (MCV)	79–100 femtoliters
White blood cell count (WBC)	4,000–11,000 cells/mm^3
Differential:	
Neutrophils	50–70% of WBC
Lymphocytes	20–40% of WBC
Monocytes	2–10% of WBC
Eosinophils	0–6% of WBC
Basophils	0–1% of WBC
Platelet count	130,000–440,000 cells/mm^3

Blood Chemistry Tests

Test	Normal Range
Electrolytes:	
Bicarbonate	22–33 mmol/L
Calcium	8.5–10.5 mg/dL
Chloride	95–105 mmol/L
Magnesium	1.5–3.0 mg/dL
Phosphorus	2.0–4.5 mg/dL
Potassium	3.5–5.0 mmol/L
Sodium	135–145 mmol/L
Liver function tests:	
ALT (SGPT)	0–50 IU/L
AST (SGOT)	0–45 IU/L
Bilirubin	0–1.5 mg/dL
Alkaline phosphatase (AP)	35–115 IU/L
GGT	30–60 IU/L
Kidney function tests:	
Blood urea nitrogen (BUN)	8–20 mg/dL
Creatinine	0.6–1.5 mg/dL
Other blood tests:	
Albumin (total serum)	3.0–5.5 g/dL
Amylase	50–160 IU/L
Creatine phosphokinase (CPK)	Men: 20–150 IU/L Women: 10–80 IU/L
Lactate (lactic) dehydrogenase	100–250 IU/L
Testosterone	Men: 200–1,200 µg/dL Women: 20–60 µg/dL

CD4 and CD8 Cell Tests

Test	Normal Range
CD4 cell count	600–1,200 cells/mm^3
High	Above 500 cells/mm^3
Medium	200–500 cells/mm^3
Low	Below 200 cells/mm^3
Treatment guidelines threshold	350 cells/mm^3
CD8 cell count	200–1,000 cells/mm^3
CD4 cell percentage	30–60%
CD8 cell percentage	15–40%
CD4/CD8 cell ratio	0.9–3.0

HIV Viral Load

Level	Normal Range
High	100,000 copies/mL or greater
Low	10,000 copies/mL or less
Undetectable	below 400 or 50 copies/mL, dependng on the test
Treatment guidelines threshold	55,000 copies/mL

Blood Sugar and Lipid Tests

Test	Normal Range
Glucose	65–125 mg/dL
Triglycerides*:	
Normal	Less than 150 mg/dL
Borderline high	150–199 mg/dL
High	200–499 mg/dL
Very high	500 mg/dL or greater
Total cholesterol*:	
Desirable	Less than 200 mg/dL
Borderline high	200–239 mg/dL
High	240 mg/dL or greater
LDL cholesterol*:	
Optimal	Less than 100 mg/dL
Near optimal	100–129 mg/dL
Borderline high	130–159 mg/dL
High	160–189 mg/dL
Very high	190 mg/dL or greater
HDL cholesterol*:	
Low	Less than 40 mg/dL
Normal (acceptable)	40–60 mg/dL
High (desirable)	60 mg/dL or greater

*(*per the National Cholesterol Education Program)*

confers resistance to current non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Phenotypic tests: these tests are done by adding a medication to an HIV culture in the laboratory to determine how much drug is needed to inhibit viral replication. Resistance levels are usually reported in terms of how much drug is needed to inhibit viral replication by 50% or 90% (the IC_{50} or IC_{90}, respectively), compared with wild-type virus. Phenotypic tests provide a more direct measure of resistance, but are more difficult, time-consuming, and expensive.

Virtual phenotype: this is a new approach to estimating the viral phenotype using a large database of more than 18,000 pairs of genotypic and phenotypic data. HIV with a similar genotype is identified in the database, and the corresponding phenotypic information is used to estimate resistance. Preliminary research suggests that the virtual phenotype predicts treatment response about as well as a true phenotypic test.

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) is used to help individualize anti-HIV therapy by measuring the amount of drug in an individual's blood. This is important because different people absorb, process, and eliminate drugs at different rates, and blood levels may vary considerably among individuals taking the same doses of the same medications. Ideally, the lowest plasma drug concentration between doses (the trough level, or C_{min}) should still be high enough to inhibit HIV, but the highest concentration (the peak level, or C_{max}) should not cause intolerable side effects.

Some, but not all, studies have shown that using TDM to guide treatment decisions increases the chance of successful viral suppression. However, drug level monitoring is not appropriate for all anti-HIV drugs. TDM has grown in popularity, especially for guiding salvage therapy, but it remains controversial and is still not widely used in the U.S. (For more on TDM and the related topics of inhibitory quotient and viral fitness, see "Salvage Therapy," *BETA*, Winter 2003; and "Therapeutic Drug Monitoring," *BETA*, Autumn 2000.)

Conclusion

Regular monitoring is an important way for HIV positive people to take control of their health. People with HIV should talk with their physicians about how often they should receive various monitoring tests. Interpretation of test results can be tricky and should be carried out by an experienced practitioner. (For this reason, we do not include a sample lab report here; some of the resources included in the sidebar on page 35 provide test result examples.)

Along with general health measures such as blood cell counts and liver enzyme levels, and specific measures of HIV disease progression such as viral load and CD4 cell count, new tests such as resistance assays and therapeutic drug monitoring may help individualize anti-HIV treatment and promote optimal outcomes.

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The Impact of Sex/Gender on Antiretroviral Therapy and Its Complications

Kathleen E. Squires, MD

Following is a modified version of an oral presentation given by Kathleen E. Squires, MD, at the 10th Conference on Retroviruses and Opportunistic Infections (CROI) held February 10–14, 2003, in Boston. It serves as an overview of the range of differences seen between women and men who have taken anti-HIV therapy. Dr. Squires explained in her opening remarks, "I have tried to distill a number of studies that have been reported and to mention some studies that I felt were illustrative, rather than attempt to be exhaustive."

Effect of Sex/Gender on Response to Antiretroviral Therapy

The first topic is sex or gender and its effect on antiretroviral therapy. There are many ways to think about response to antiretroviral therapy. I want to consider first the now classic parameters, or endpoints, looked at in clinical trials, specifically virologic and immunologic response. In other words, what is the effect of therapy on viral load and CD4 cell counts? I will use as an example the study called Women First. Though it was performed several years ago, Women First was the first trial—at least that I am aware of—that was designed to look specifically at the effect of antiretroviral therapy in a group of women, using what was considered at the time to be a very rigorous type of regimen. By offering the best therapy then available to this group of women, the study researchers tried to answer the question: can women take antiretroviral therapy successfully? As we all know, women traditionally have been underrepresented in clinical trials. There are many reasons for this, one being the assumption that women, because of other issues in their lives, cannot adhere to complicated regimens. This assumption, among others, was examined in Women First.

In terms of virologic and immunologic response, about 65–80% of subjects in this study were able to achieve a viral load of fewer than 400 or 50 copies/mL. They also experienced CD4 cell count increases of anywhere from 175 to 225 cells/mm^3, depending on the arm of the study. Nelfinavir [Viracept] and saquinavir [Fortovase or Invirase] were given in combination—not a combination that we give at the present time—with two nucleoside analogs [NRTIs] given either twice or three times daily. Responses in this group of women were therefore similar to those that were reported in concurrent antiretroviral studies enrolling mostly men. But another important conclusion was that women can enroll and participate and be maintained successfully in clinical trials when they see that the treatment under study is interesting to them and likely to be beneficial.

Data from further studies in which gender analyses were performed have shown that, overall, there are no significant differences in outcomes between men and women in terms of classic clinical trial parameters: the percentage of patients who are able to achieve HIV RNA [viral load] levels of fewer than 400, 200, or 50 copies/mL, depending on the particular trial; CD4 cell count increases over baseline; time to virologic failure; and response to therapy. These specific gender analyses have been performed with regimens that are used at the present time, namely triple combination regimens with protease inhibitor [PI] or non-nucleoside reverse transcriptase inhibitor [NNRTI] backbones.

In recent years a number of cohort studies have also compared response rates between women and men after adjusting for factors that might be considered confounding

variables, such as age, race, education, injection drug use, CD4 cell count, and viral load before the initiation of anti-HIV therapy. Results from these studies mirror the gender analyses performed in the antiretroviral trials.

I will mention one such cohort study, an analysis of women and men initiating antiretroviral therapy in a university-based clinic, which was presented at last year's Retrovirus conference [poster 777-W]. Baseline CD4 cell counts among the 80 women and 149 men were similar [a mean of 130 cells/mm^3], while viral load was lower in the women. A lower baseline viral load in women is a consistent phenomenon that is seen across cohort studies and clinical trials. Interestingly, the time to initiation of antiretroviral therapy in this study was longer in women than in men [355 vs 184 days], and women were more likely to achieve undetectable viral loads. The CD4 cell response and the durability of response for both CD4 cell count and viral load were very similar.

A few other clinical trials have reported that higher proportions of women achieve virologic success [undetectable viral load] compared with men. The fact that women on average have a lower viral load at the time they start therapy would certainly contribute to such an outcome.

The key message in terms of response to antiretroviral treatment is that there seem to be no substantial differences between women and men among those who are able to take therapy. This has no doubt influenced the substantial benefit seen with the advent of antiretroviral medication, and specifically highly active antiretroviral therapy [HAART]-based regimens, in the parts of the world where there is access to these drugs. Again, one caveat in terms of these response rates is whether patients are able to tolerate and maintain their drug regimens.

Effect of Sex/Gender on Antiretroviral Pharmacokinetics

Next, I would like to consider how women and men differ in terms of a variety of pharmacokinetic factors. [Pharmacokinetics refers to the metabolism, absorption, and elimination of drugs in the body.]

Studies have shown that several of these factors are likely to have an impact on anti-HIV therapy. For example, we know that women on average have lower body weight and higher body fat content than men. There are clear hormonal differences between women and men. In pregnant HIV-infected women the differences in volume and distribution of antiretroviral agents need to be considered. Differences in hepatic [liver] function are related to the cytochrome P450 enzyme system, which metabolizes several anti-HIV drugs. The CP450 enzyme system is made up of an array of specific enzymes [proteins that act as catalysts] called isoenzymes; women and men have a relatively different distribution and percentage of these isoenzymes. And then there is the important issue of drug interactions.

DRUG EXPOSURE AND TOXICITY

A 2001 report by David Burger, PhD [University Hospital Nijmegen], and colleagues included a gender analysis of a therapeutic drug monitoring [TDM] database looking specifically at indinavir [Crixivan] concentrations. [TDM involves measuring drug levels in the blood to ensure the most potent response with a minimum of adverse events.] The researchers found no statistically significant difference between indinavir concentration ratios in women and men.

However, when they considered adverse events attributed to indinavir—hyperbilirubinemia [high bilirubin levels in the blood] and especially renal [kidney] effects, which they called "intoxification"—TDM was indicated for a much higher proportion of women [17.4%] than men [6.6%], a statistically significant difference. The indication for TDM likewise led to a dose reduction due to side effects in a higher proportion of women [9.7%] than men [1.1%]. So there appears to be a relationship between gender, drug exposure, and toxicity.

EFFECT OF SEX AND BODY WEIGHT ON PHARMACOKINETICS

A pharmacological substudy of ACTG 359, which compared salvage regimens for patients whose indinavir-containing regimens had failed, was presented by Richard Brundage, PharmD [University of Minnesota], and colleagues at the 2002 Retrovirus conference. The substudy showed that ritonavir [Norvir] coadministration with saquinavir and nelfinavir led to a three-fold increase in saquinavir exposure compared with nelfinavir across the group as a whole. However, saquinavir clearance in women was reduced by 50%, and it appeared that weight was positively correlated with this outcome. At the least, this study shows that perhaps there are gender issues in terms of a weight differential, and that weight does affect serum drug levels.

DOSE MODIFICATION

Also worth mentioning is the effect of sex or gender and body weight on antiretroviral dose modification. Data from a gender analysis of ACTG 175, which has been presented by Judith Currier, MD [University of California, Los Angeles], and colleagues, demonstrated higher rates of dose modification for women who were randomized to the ddI [didanosine, Videx] arm than men randomized to the same arm. Women in the study were more likely than men to weigh 60–65 kg [132–143 lbs] and hence, on average, to receive the higher dose of ddI on a milligram per kilogram basis; the weight cut-off for dose reduction of this particular drug is 60 kg. In a logistic regression analysis, this result was related in part to a weight difference.

So, while differences in weight between women and men can perhaps lead to toxicity, this study shows that such differences can also result in variances in terms of dose modification.

DRUG INTERACTIONS WITH ORAL CONTRACEPTIVES

Oral contraceptives are commonly used by HIV positive women, and hormone replacement therapy [HRT] by those who are postmenopausal. While we are all aware of changing attitudes as far as using HRT, if we are going to use oral contraceptives in HIV-infected women, we need to understand that there are significant drug interactions between oral contraceptive agents and the PI and NNRTI drug classes. For example, study data have shown that nelfinavir and ritonavir decrease levels of the oral contraception pill [OCP, or "the Pill"] and should not be used in women taking OCP. The same is true of nevirapine [Viramune], which has been shown to cause estrogen AUC levels to drop by 19%. [AUC refers to area under the curve, a measure of total drug concentration over time.]

This is by no means an exhaustive account of drug interactions that have been studied, but it clearly indicates that women who use oral contraceptives need to have their combination regimens carefully selected. Unfortunately, no guidance for dose modification of oral contraceptives when used with HAART is currently available.

Sex/Gender and Complications Associated with HAART

Research data suggest that differences exist between women and men in terms of complications associated with antiretroviral agents. On a positive note, it appears that women have a lower risk for triglyceride increases with the use of some anti-HIV agents. However, an increased incidence of pancreatitis [inflammation of the pancreas] has been seen in women, and they have an increased risk for hepatic steatosis [fat buildup and subsequent tissue degeneration in the liver] and lactic acidosis [a life-threatening buildup of lactic acid in cells]. In the realm of body shape changes, women across a number of studies have shown a greater risk for fat accumulation and breast enlargement. I have a question about decreased bone mineral density, and fortunately we are now beginning to see some bone-related studies in HIV-infected women. Finally, it appears that women are at increased risk for rash, specifically NNRTI-associated rash.

RASH AND HEPATOTOXICITY

Starting with the issue of nevirapine hepatotoxicity [liver toxicity] as well as nevirapine-associated rash, I will refer to the results of the FTC-302 trial reported in 2001, in which nevirapine and efavirenz [Sustiva] were compared with each other together with a backbone of NRTIs, including FTC [emtricitabine, Emtriva]. Ten percent of subjects in this trial experienced grade 4 [life-threatening] liver enzyme elevations, and the incidence of these grade 4 elevations was two times greater in women than in men. Two fatalities were reported in the study, both of which occurred in women who experienced liver enzyme elevations, although other clinical factors may have been responsible.

In other studies looking at the issue of nevirapine toxicity, women have not been shown to have an increased risk of hepatotoxicity. In addition, I was fortunate to see the data set that Boehringer Ingelheim [the manufacturer of nevirapine] has put together looking across all of their nevirapine trials, as well as cohorts and other clinical trials that have used this drug. The overall conclusion from their rather large data set is that female sex is not an independent risk factor. So there is some controversy around this issue. Nevertheless, the FTC-302 study was compelling, and the results should be kept in mind as nevirapine is commonly used in HIV-infected women.

As for nevirapine-associated rash, I will mention a study reported by Judith Aberg, MD [Washington University], looking at two clinic populations and showing that rash was significantly more common in women. A number of other studies in the literature also show that rash is more commonly reported in women taking nevirapine than in men. In fact, in the Boehringer Ingelheim data set female sex does fall out as an independent risk factor for nevirapine-associated rash. Such data need to be considered when using this particular agent in women.

PANCREATITIS

What about pancreatitis? At least one report in the literature features an analysis of adverse events related to NRTI use in a large urban HIV clinic at Johns Hopkins University, in patients who were receiving NRTIs with or without hydroxyurea [Hydrea]. In a multivariate analysis, female sex was an independent risk factor for pancreatitis. There are other isolated reports in the literature also suggesting a difference in risk between women and men.

ADVERSE EVENTS RELATED TO PARTICULAR DRUGS

Looking at adverse events related to particular drugs, I have tried to summarize data gathered several years ago focusing on the PIs ritonavir and nelfinavir. In the case of ritonavir, the definition of intolerance was abdominal pain, nausea, vomiting, and circumoral [around the mouth] numbness. It appeared that women experienced these side effects more commonly than men.

In the case of nelfinavir, an analysis of the combined data from three registrational trials indicated that women were less likely to experience grade 2 [moderate, persistent] diarrhea than men; this result also has been shown in more recent studies. Yet in these same trials abdominal pain, pruritis [itching], and rash were more commonly seen in women. Data in the literature therefore suggest differences in the incidence, frequency, and types of adverse events seen in women compared with men with the use of these agents.

SERUM LIPID ABNORMALITIES

As I have mentioned, women may have an advantage in the case of serum lipid [blood fat] abnormalities. START I and START II, two trials in which specific sex or gender analyses were done, compared different NRTI backbones—

d4T [stavudine, Zerit]/ddI, d4T/3TC [lamivudine, Epivir], and AZT [zidovudine, Retrovir]/3TC—given in combination with indinavir. Both START studies showed that across all of the NRTI arms, women were less likely to experience grade 1 to 4 [mild to life-threatening] elevations of serum triglycerides than men.

There is also a gender analysis that we have done of the Glaxo Wellcome-sponsored trial ESS4001, presented at last year's Retrovirus conference. This was a comparison of a triple NRTI regimen vs a PI-based regimen using nelfinavir, and a comparison of AZT/3TC vs d4T/3TC as an NRTI backbone. Again, women were less likely to experience triglyceride elevations than men across the three arms of the study. Data from other studies substantiate these results.

LACTIC ACIDOSIS

Lactic acidosis is a severe complication of antiretroviral therapy associated with a rather high mortality rate. In a Food and Drug Administration [FDA] review of 107 reported cases presented in 1999, lactic acidosis was associated with dual NRTI use. Thirty [83%] of the cases occurred in women, 50% of whom weighed 175 lbs or more, and in that whole series the mortality rate was 55%.

Single case reports as well as small case series of lactic acidosis have been reported over the past decade. I now have a fellow working with me doing a retrospective analysis of all reported cases of the condition, and although I have not looked at every one of them, we have a pretty complete data set. Our calculations indicate that over 80% of all cases in which sex was reported occurred in women. Women thus appear to be much more commonly affected by this complication.

LIPODYSTROPHY

I have tried to distill data from lipodystrophy studies looking at women only, as well as comparing women and men in terms of lipoatrophy [fat loss], central adiposity [fat gain in the abdomen], and mixed syndrome [fat loss and gain in different body areas of the same person]. From the data gathered so far, fat accumulation is more common in women, while fat depletion is more commonly seen in men. The prevalence of mixed syndrome appears to be equivalent in women and men. Since the definition of lipodystrophy is still changing, future studies might help us more clearly identify differences that exist between women and men in terms of body fat irregularities.

OSTEOPENIA AND OSTEOPOROSIS

The earliest studies looking at the effect of antiretroviral therapy and/or HIV infection on rates of osteopenia and osteoporosis [reduced bone mineral density] were pursued exclusively in men. We now have data, including some presented at this conference, looking at bone mineral density specifically in women. Yet results to date are conflicting as to whether osteopenia and osteoporosis are more commonly seen in HIV positive women as opposed to HIV negative women, and whether antiretroviral therapy such as PI use increases the risk. We need to look at more studies coming out on this issue for definitive answers.

Summary

In summary, response to antiretroviral therapy is similar in women and men; an equal virologic and immunologic benefit is seen in patients of both sexes who can tolerate these drugs. There are differences in pharmacokinetic parameters, however, that lead to disparities in drug levels and toxicities between women and men. There are also sex- and gender-based differences in adverse events and drug and HIV-associated complications. The overall efficacy and success of anti-HIV regimens may be impaired as a result of these various differences. I would like to suggest that we carry out prospective studies designed to define optimal antiretroviral regimens for HIV-infected women.

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RESOURCES

WORLD (Women Organized to Respond to Life Threatening Disease) is an information and support network by, for, and about women with HIV/AIDS.
Visit *www.womenhiv.org* or call 510-986-0340.

The Body's Forum on Women and HIV, which includes an "ask the experts" advice column, can be viewed at *www.thebody.com/Forums/AIDS/Women.*

Project Wise is a program of Project Inform focusing on HIV/AIDS treatment information and advocacy for women. For information about Project Wise and to subscribe to its publication, *Wise Words,* visit *www.projectinform.org.*

OPEN Clinical TRIALS FOR HIV/AIDS TREATMENTS

Liz Highleyman

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

The federal government's AIDSinfo site (which replaced the former ACTIS and HIVATIS sites) features study listings from the ClinicalTrials.gov database of trials for all diseases maintained by the National Institutes of Health (NIH). The AIDSinfo site is available at *www.aidsinfo.nih.gov.* AIDSinfo also offers a toll-free telephone information line at 800-448-0440 (TDD/TTY 888-480-3739; international callers should dial 301-519-0459). Health information specialists are available Monday through Friday from 12:00 pm to 5:00 pm ET (9:00 am to 2:00 pm PT).

The AIDS Community Research Initiative of America (ACRIA) maintains a listing of HIV/AIDS clinical trials in the Mid-Atlantic region, and may expand to other areas in the future. The listing is available at *www.criany.org.*

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

OPTIMA: Mega-HAART and STI

This study will examine the benefits of mega-HAART regimens in people with advanced HIV disease for whom anti-HIV treatment with the first three drug classes—nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs)—has failed. It will also look at whether a three-month break from treatment can help reduce drug resistance and allow people to better tolerate therapy. Participants will be randomized to either begin treatment immediately or undergo a three-month drug-free period. Once treatment begins, some subjects will be randomized to receive mega-HAART regimens containing five or more anti-HIV drugs, while others will take standard HAART regimens of up to four drugs. Outcomes to be measured include viral load, immunological function, time to serious adverse events, time to AIDS-defining illness, and survival time. About 1,700 participants will be followed for an average of two years.

Participants must be at least 18 years of age. They must have been on continuous HAART for at least three months, and must be on therapy at the time of enrollment. In addition, they must have experienced viral breakthrough with at least two different multidrug regimens that included NRTIs, NNRTIs, and PIs, or have laboratory test results that show resistance to drugs in each of these classes. The two most recent measurements while on the current regimen must have shown a CD4 cell count of 300 cells/mm^3 or less and a viral load above 2,500 or 5,000 copies/mL (depending on the test used). Subjects are ineligible if they are unable to tolerate multiple antiretroviral drugs or have had serious

opportunistic illnesses (OIs) within 14 days of screening. Women may not be pregnant or breast-feeding.

The study will be conducted at 26 Veterans Administration medical centers, including **Baltimore** (410-605-7199), **Boston** (617-232-9500 ext. 4669), **the Bronx** (718-584-9000 ext. 6671), **Dallas** (214-857-0410), **Los Angeles** (310-268-3015), **Miami** (305-324-4455 ext. 4800), **Palo Alto** (650-493-5000 ext. 63408), **Philadelphia** (215-823-5847), **Phoenix** (602-277-5551 ext. 6796), and **San Diego** (858-552-8585 ext. 2626); *www.clinicaltrials.gov/ct/show/NCT00050089.* (CSP 512)

Salvage Therapy: Amdoxovir plus T-20

This randomized, placebo-controlled trial will test the safety and effectiveness of adding one or two new drugs in treatment-experienced people using a failing antiretroviral regimen. Participants will add either T-20 (enfuvirtide, Fuzeon) alone or T-20 plus amdoxovir (DAPD) to an optimized background regimen. Subjects must be on a failing regimen at the time of study entry. They will then begin taking a regimen containing at least three but not more than five drugs, selected with the aid of resistance test results. The study will supply amdoxovir and T-20, but not the other drugs in the regimen. Participants will be taught how to self-inject T-20. Study visits will take place at weeks 1, 2, and 4, then every four weeks until week 48. At the 4-week visit pharmacokinetic testing will be done, which will require participants to remain at the clinic for approximately 12 hours.

Participants must be at least 18 years of age. They must have used at least two combination antiretroviral regimens for a total of 24 months; regimens must have included at least two NRTIs, two PIs, and one NNRTI, and at least two of the previous multidrug regimens must have failed. Subjects must have a viral load of at least 5,000 copies/mL while on stable (unchanged) treatment within 60 days of study entry. Participants may not previously have used amdoxovir or T-20, nor recently have received experimental drugs, immune-modulating drugs, or vaccines. People with serious illnesses, unexplained fevers, diabetes, cancer requiring chemotherapy, or a history of kidney stones or certain types of vision loss are ineligible. Participants must be willing to use birth control, if appropriate, and women may not be pregnant or breast-feeding.

Study sites are in **Cleveland** (216-778-5489 or 216-844-8051), **Denver** (303-372-5535), **New York City** (212-746-4393 or 212-305-2665), and **San Juan, Puerto Rico** (787-767-9192); *www.clinicaltrials.gov/ct/show/NCT00031044.* (ACTG A5118)

RESIST: Tipranavir

The Phase III RESIST 1 and 2 trials, sponsored by pharmaceutical manufacturer Boehringer Ingelheim, will study use of the experimental nonpeptidic PI tipranavir in heavily treatment-experienced subjects who have used NRTIs, NNRTIs, and PIs. Researchers hope that tipranavir will be active against HIV that has developed resistance to other PIs. RESIST 1, a randomized, open-label study, will compare the safety and effectiveness of tipranavir boosted with low-dose ritonavir (Norvir) against that of another PI (also boosted with ritonavir) chosen by participants' doctors on the basis of treatment history and resistance testing. All subjects will receive resistance tests upon study entry to allow selection of an optimal background regimen. Those randomized to tipranavir will receive a dose of 500 mg tipranavir plus 200 mg ritonavir twice daily. The study will last 48 weeks, with an extension phase of the same duration.

Eligible participants must be at least 18 years of age and must be on a regimen that includes a PI. They must have previously taken at least two PIs and at least one NRTI and NNRTI for three months or more. At study enrollment they must have at least one primary PI resistance mutation, but should not be resistant to all comparable PIs (amprenavir [Agenerase], indinavir [Crixivan], lopinavir [Kaletra], and saquinavir [Fortovase]). Viral load must be at least 1,000 copies/mL; there is no CD4 cell count requirement. There are additional criteria related to blood lipid (fat) and liver enzyme levels. Participants are not eligible if they have previously taken tipranavir, have recently used other investigational drugs (except the recently approved T-20 or atazanavir [Reyataz]), or have used immune-modulating drugs within 30 days of study entry. Women must be willing to use a barrier method of contraception and may not be pregnant or breast-feeding. Some study sites are running companion trials for treatment-experienced people who do not qualify for RESIST 1.

RESIST 1 will enroll 500 participants in the U.S., Canada, and Australia. (RESIST 2 will include 800 subjects in Europe and South America.) There are some 80 sites in the U.S. For more information and a list of sites, call Veronika Kohlbrenner at 800-344-4095 ext. 6215, or see *www.clinicaltrials.gov/ct/show/NCT00054717.* (BI1182.12)

Therapeutic Drug Monitoring

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

an NIQ of 1 or less will be randomized to receive either standard antiretroviral therapy (arm A) or adjusted doses of drugs based on TDM test results (arm B). Those with an NIQ greater than 1 will be randomized either to an observational arm (arm C) or to discontinue the study. Subjects in any arm who experience virological failure after the first week will be eligible to receive a second resistance test.

Participants must be at least 18 years of age and have a viral load of 2,000 copies/mL or more at study screening and at least one viral load measurement of 400 copies/mL or more within 60 days of study entry. Subjects must be experiencing viral breakthrough on a second, third, or fourth HAART regimen, each of which consisted of at least three but less than six drugs; at least one failing regimen must have included a PI. Participants must have been on their current regimen for at least 12 weeks prior to study entry. Subjects may not have an acute illness requiring treatment within 21 days of study entry, cancer requiring radiation or chemotherapy, or a history of pancreas problems. They should not have recently received experimental drugs, immune-modulating drugs, or HIV vaccines, and may not have ever used a previous mega-HAART regimen containing more than six drugs. Participants must be willing to use birth control, if appropriate, and women may not be pregnant or breast-feeding.

There are 35 study sites, including **Boston** (617-632-0785), **Chicago** (312-572-4545), **Denver** (303-372-5535), **Honolulu** (808-737-2751), **Indianapolis** (317-630-6023), **Los Angeles** (310-206-8029), **Miami** (305-243-3838), **Nashville** (615-467-0154 ext. 108), **New York City** (212-263-6565), **Pittsburgh** (412-647-0771), **Rochester** (585-275-2740), **San Francisco** (415-514-0550 ext. 362), **Seattle** (206-731-8877), and **St. Louis** (314-454-0058); *www.clinicaltrials.gov/ct/show/NCT00041769.* (ACTG A5146)

TDM and Lopinavir

This randomized, controlled, Phase II study will look at whether adjusting doses of lopinavir/ritonavir (Kaletra) using therapeutic drug monitoring results can help lower viral load in treatment-experienced people on failing antiretroviral therapy. Participants will be randomized to receive either standard doses of lopinavir or concentration-adjusted doses based on measurements of blood drug levels and resistance tests. All subjects will start taking an antiretroviral regimen of lopinavir, tenofovir DF (Viread), up to two NRTIs, plus either amprenavir or saquinavir. Only lopinavir, tenofovir, and saquinavir will be provided by the study. Participants in arm B will take the usual approved dose of lopinavir for 14 days, then will receive a 12-hour series of blood drug level measurements. If their blood levels of lopinavir are too low, additional ritonavir will be added to further boost lopinavir levels. Drug monitoring and dose adjustment will be repeated, if needed, at week 5. Subjects in arm A will receive similar blood drug level monitoring and dose adjustment if they have high viral load levels at week 24. Clinic visits are weekly through week 6, then at week 8, then every four weeks through week 48.

Eligible participants must be at least 18 years of age and have had a viral load of at least 5,000 copies/mL and a resistance test showing reduced sensitivity to lopinavir within 45 days of study entry. They must have been on stable antiretroviral therapy including at least one PI for 12 weeks before entering the study, and have previously used two or more NRTIs for at least six months each. Participants may not have used certain drugs, including NNRTIs, within 14 days of study entry. Subjects are ineligible if they have recently had a serious illness, unexplained fever, cancer requiring chemotherapy, or recent use (within 30 days) of immune-modulating drugs, experimental agents, or HIV vaccines. They may not use PIs other than lopinavir, amprenavir, or saquinavir during the study. Participants must be willing to use birth control, if appropriate, and women may not be pregnant or breast-feeding.

Study sites are in **Cleveland** (216-844-8051), **Galveston** (215-349-8092), **Miami** (305-243-3838), **New York City** (212-263-6565), and **Pittsburgh** (412-647-0771); *www.clinicaltrials.gov/ct/show/NCT00046033.* (ACTG A5135)

SMART: Drug Conservation vs Viral Suppression

The SMART study, conducted by the Community Programs for Clinical Research on AIDS (CPCRA), is a large, simple trial comparing two HIV treatment strategies. The study will attempt to determine whether participants at low risk of disease progression can safely reduce their use of anti-HIV therapy, thus minimizing side effects, staving off drug resistance, and conserving treatment options. Participants randomized to the drug conservation arm will stop (or not start) anti-HIV therapy until their CD4 cell counts fall below 250 cells/mm^3, at which point they will begin therapy and continue until their CD4 cell counts rise above 350 cells/mm^3. Those randomized to the viral suppression arm will continue (or start) treatment in an attempt to keep viral load as low as possible, regardless of CD4 cell count. Participants will be seen at months 1, 2, 4, 6, 8, 10, and 12 after study entry, and every four months thereafter. Some 6,000 participants will be followed for an estimated 6–9 years, until 910 primary events (disease progression or death) occur. Selected subsamples of participants will be followed with more intensive data collection for secondary outcomes related to cost, health-care utilization, metabolic complications of treatment, and quality of life.

Participants must be at least 13 years of age and have a CD4 cell count above 350 cells/mm^3 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. Participants must be willing to use

birth control, if appropriate, and women may not be pregnant or breast-feeding.

There are more than 60 study sites, including **Boston** (617-778-5454), **Brooklyn** (718-270-4487), **Chicago** (773-244-5802), **Denver** (303-436-7195), **Detroit** (313-745-4431), **Houston** (713-500-6751), **Newark** (973-483-3444), **New Orleans** (504-584-1971), **New York City** (212-939-2957), **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.* (CPCRA 065)

HIV Progression after Antiretroviral Discontinuation

Current federal HIV treatment guidelines recommend that therapy should be started when CD4 cell counts fall below 350 cells/mm^3. Recent research suggests that people with CD4 cell counts above this level may be able to safely discontinue antiretroviral treatment. This prospective, observational trial will look at immunological, virological, and clinical progression of HIV disease in people with low viral loads and CD4 cell counts above 350 cells/mm^3 who stop antiretroviral therapy. At the first study visit, participants will receive a blood draw and baseline body measurements. They will then discontinue their anti-HIV therapy. Study visits will take place every 4–8 weeks for one year, then every 12 weeks for a second year. Viral load, CD4 cell counts, immunological function, neurocognitive (mental) changes, metabolic measurements, body shape changes, health-care utilization, and quality of life will be assessed over the course of the study. Participants and their physicians will decide if and when to restart anti-HIV therapy; those who do so will be followed for at least an additional 24 weeks. This study does not provide any medications.

Participants must be at least 13 years of age and have been receiving stable antiretroviral treatment with two or more drugs for at least six months prior to study entry. They must have a pretreatment CD4 cell count above 350 cells/mm^3; in addition, they must have a CD4 cell count above 350 cells/mm^3 and a viral load below 55,000 copies/mL within 45 days of study entry. Subjects are ineligible if they have cancer requiring chemotherapy or have taken immune-modulating or experimental drugs within 30 days of study entry. Use of adefovir (Hepsera) or tenofovir is not permitted. Severe illness, relevant chronic medical conditions, and certain AIDS-related illnesses are excluded. Women may not be pregnant or breast-feeding.

There are more than 30 study sites, including **Chicago** (312-695-5012), **Dallas** (214-590-0414), **Los Angeles** (310-222-3848), **Minneapolis** (612-625-1462), **New York City** (212-420-4432), **Pittsburgh** (412-647-0771), **Providence** (401-793-4396), **San Diego** (619-543-8080), **San Francisco** (415-514-0550), and **Washington, DC** (202-687-7387); *www.clinicaltrials.gov/ct/show/NCT00050284.* (ACTG A5170)

When to Change Therapy

This randomized pilot study will compare participants who change antiretroviral therapy when their viral load reaches 200 copies/mL against those who switch when their viral load reaches 10,000 copies/mL. The trial will look at drug resistance, viral fitness, and immune reconstitution. Current federal guidelines recommend switching to a new regimen as soon as viral load starts to rise in order to minimize the development of drug resistance. But there is evidence that some people can still benefit from therapy even after viral rebound, and delaying a regimen switch may help preserve future treatment options. Participants in this study with viral loads between 200 and 10,000 copies/mL will be randomized to immediate-switch (arm A) or delayed-switch (arm B) groups. Subjects in arm A will receive genotypic resistance testing upon study entry and, based on these results, will switch to a new regimen within four weeks. Subjects in arm B will continue their current regimen and receive resistance testing when their viral load reaches 10,000 copies/mL or more; based on the resistance test results, they will then change their regimen. Resistance testing and regimen switching will also take place if CD4 cell counts decline by 20% from baseline. All participants will be followed for at least 48 weeks. This study provides no drugs.

Eligible participants must be at least 13 years of age and have been on stable HAART for at least four months. They must have a CD4 cell count of 200 cells/mm^3 or greater within 45 days of study entry. Viral load must be detectable on the current regimen within 52 weeks prior to screening, and must have been below 500 copies/mL any time prior to screening while on the same regimen. Subjects may not have an infection or cancer requiring treatment within 45 days of study entry, and may not recently have received experimental drugs, corticosteroids, immune-modulating drugs, or an HIV vaccine. Participants must be willing to use birth control, if appropriate, and women may not be pregnant or breast-feeding.

There are 20 study sites, including **Boston** (617-726-3819), **Chicago** (312-942-5865), **Dallas** (214-590-0414), **Denver** (303-372-5535), **Durham** (919-668-0161), **Miami** (305-243-3838), **Nashville** (615-467-0154), **New York City** (212-263-6565), **Pittsburgh** (412-647-0771), **Seattle** (206-731-8877), and **Stanford** (650-723-2804); *www.clinicaltrials.gov/ct/show/NCT00036465.* (ACTG A5115)

Niacin and Garlic for Hyperlipidemia

Because it can contribute to heart disease, hyperlipidemia (elevated blood fat levels) is among the most worrisome adverse effects associated with HIV disease and its treatment. Two studies are looking at ways to reduce elevated cholesterol and triglyceride levels in HIV positive people.

I) The first study will evaluate the safety, effectiveness, and tolerability of extended-release niacin (Niaspan) in reducing blood fat levels. Niacin is commonly used to treat hyperlipidemia in the HIV negative population. In this non-randomized, open-label study participants will first begin a lipid-lowering diet and exercise program that will continue for the 48 weeks of the study. After four weeks, subjects will begin taking extended-release niacin, escalating doses every 4–6 weeks over a 16-week period. At weeks 14 and 20 the adequacy of the niacin dose will be determined by measuring blood fat levels and adjusted if necessary; participants will remain on the 20-week dose for the remainder of the study. If blood fat levels have not improved significantly by week 24, subjects may add another lipid-lowering drug. Clinic visits will take place at weeks 4, 8, 12, 18, 24, 32, 40, and 48; participants must fast for 8–12 hours before visits that include a blood draw.

Eligible participants must be at least 18 years of age and on a stable HAART regimen for at least three months. They must have a fasting non-HDL cholesterol level of 180–250 mg/dL or more (but an LDL cholesterol level not exceeding 200 mg/dL) and a serum triglyceride level of 200 mg/dL or more within 30 days of study entry. Participants may not have coronary heart disease, cerebrovascular disease, congestive heart failure, uncontrolled high blood pressure, acute gout, peptic ulcers, diabetes that must be controlled by diet or drugs, untreated hypothyroidism, gallbladder disease, cancer, or active OIs. They may not have taken niacin or any other lipid-lowering medications within 30 days, or chemotherapy, glucocorticoids, immune-modulating drugs, or certain diabetes medications within 60 days of study entry. Participants must be willing to use birth control, if appropriate, and women may not be pregnant or breastfeeding. Oral contraception and stable hormone replacement therapy are allowed.

There are 15 study sites, including **Cincinnati** (513-584-8373), **Denver** (303-372-5535), **Indianapolis** (317-630-6023), **Los Angeles** (310-206-8029), **Miami** (305-243-3838), **Pittsburgh** (412-647-0771), **Stanford** (650-723-2804), and **St. Louis** (314-454-0058);
www.clinicaltrials.gov/ct/show/NCT00046267.
(ACTG A5148)

II) The second study is a randomized, placebo-controlled trial of dried garlic powder (Garlicin brand *Allium sativum,* or allicin) to lower cholesterol and triglyceride levels in hyperlipidemic participants on HAART. Bastyr University's Alternative Medicine Care Outcomes in AIDS study has found that garlic is the most common herbal therapy taken by people with HIV who use complementary and alternative medicine, and a growing body of research indicates that garlic has lipid-lowering effects. Participants will be randomized to receive one of two escalating doses of garlic supplements. Total serum cholesterol, triglycerides, blood glucose, insulin, and liver enzyme levels will be measured.

Eligible participants must be between 18 and 65 years of age and on stable HAART for at least six months prior to study entry. They must have a CD4 cell count of 100 cells/mm^3 or greater within 60 days of study entry and viral load below 2,000 copies/mL. Cholesterol levels must be at least 200 mg/dL and triglyceride levels must be between 250 and 1,000 mg/dL. Participants must be willing and able to avoid raw or dried garlic, onions, leeks, and shallots during the 16-week study.

The study will be conducted at Bastyr University's Center for Natural Health in **Seattle** (425-602-3170);
www.clinicaltrials.gov/ct/show/NCT00029250.
(1 R01 AT00328-01)

Triple Infection with Hepatitis: HIV/HBV/HCV

Coinfection with HIV and chronic hepatitis B or C is a growing public health concern, and there is convincing evidence that HIV infection accelerates the progression of liver disease due to viral hepatitis. To date, however, many studies of treatments for hepatitis B and C have excluded people with HIV. This randomized, placebo-controlled Phase II study will investigate the safety and effectiveness of a combination drug regimen in people triply infected with the hepatitis B virus (HBV), the hepatitis C virus (HCV), and HIV. The trial will also evaluate the effect of HBV and its treatment on HCV and HIV disease progression. Participants will be randomized to one of two treatment arms for 48 weeks. Both groups will receive daily oral ribavirin and weekly injections of pegylated interferon, and all participants must be taking 3TC (lamivudine, Epivir). Subjects in arm A also will receive daily adefovir, while those in arm B will receive a placebo (inactive pill). After 48 weeks all study medications will be discontinued and subjects will receive a liver biopsy. They will then be followed for an additional 24 weeks.

Eligible participants must be between 18 and 65 years of age. They must have a detectable HCV viral load within 48 weeks and an HBV viral load of at least 50,000 copies/mL within 12 weeks of study entry. CD4 cell count must be at least 200 cells/mm^3 and HIV viral load must be below 55,000 copies/mL within 35 days of study entry. Subjects must have been treated with 3TC for at least 26 weeks prior to study entry and must have documented 3TC-resistant HBV. In addition, they must have been on stable HAART for at least 12 weeks prior to the study and plan to remain on that regimen, or else not have received HAART in the prior 12 weeks and not plan to start during the first 12 weeks of the study. Participants are not eligible if they have a history of chronic liver disease other than viral hepatitis; severe liver enzyme elevations; advanced liver damage; a history of suicide attempts or hospitalization for psychiatric illness within two years (depression and anxiety are known side effects of interferon therapy); an uncontrolled seizure disorder; autoimmune disorders; cancer; OIs; or heart, lung, or

kidney disease. Certain medications are excluded. Participants must be willing to use birth control, if appropriate, and women may not be pregnant or breast-feeding.

Study sites are in **Birmingham** (205-975-7925), **Cincinnati** (513-584-8373), **Denver** (303-372-5535), **Galveston** (409-747-0241), **New York City** (212-695-5012), and **San Francisco** (415-514-0550 ext. 354); *www.clinicaltrials.gov/ct/show/NCT00051077*. (ACTG A5149)

Non-Hodgkin's Lymphoma

Treatment for non-Hodgkin's lymphoma (NHL) is often difficult in people with HIV because chemotherapeutic drugs used to treat the cancer can further suppress the immune system and increase the risk of infection. Several studies are underway looking at new drug regimens for HIV positive people with NHL.

I) A National Cancer Institute (NCI) study will evaluate the safety and effectiveness of a short course of chemotherapy known as EPOCH plus rituximab (Rituxan, a monoclonal antibody) to treat NHL in HIV positive people. The typical course of EPOCH/rituximab is six weeks. This study will look at whether reducing the total amount of chemotherapy can rid the body of lymphoma quickly, while decreasing the risk of infections and future cancers. At study entry a battery of screening tests including bone marrow biopsy, lumbar puncture (spinal tap), and various imaging tests will be done to determine the location and extent of the lymphoma. Participants will then receive outpatient chemotherapy for 6–18 weeks in three-week cycles consisting of oral prednisone and intravenous etoposide, doxorubicin, and vincristine on days 1–5, and intravenous cyclophosphamide on day 5. Rituximab will be infused on days 1 and 5. Starting on day 6, subjects will receive no chemotherapy for 16 days. Imaging scans will be done to assess progress after each cycle. If lymphoma goes into complete remission, treatment will be stopped after one further cycle; no subjects will receive more than six cycles. Participants will be followed for 24 months.

Eligible participants must be at least 13 years of age and have aggressive CD20+ NHL. They must not have previously used rituximab or certain types of chemotherapy. Various laboratory test criteria must be met. Anti-HIV therapy will be suspended before chemotherapy is started, and will be reinitiated after all the cycles have been administered. Subjects must not have serious medical conditions, symptomatic heart disease, severe wasting, or untreated central nervous system OIs. Women may not be pregnant or breast-feeding.

The study will be conducted at the National Cancer Institute in **Bethesda** (888-624-1937), and enrolled participants will be reimbursed for travel to the study site; *www.clinicaltrials.gov/ct/show/NCT00006436*. (010030; 01-C-0030)

II) A second NCI study will look at the EPOCH/rituximab combination in HIV positive people with untreated B cell NHL. In this randomized, open-label Phase II study, some participants will receive rituximab concurrently with the chemotherapy drugs (2–4 hours prior to each cycle), while other subjects will receive rituximab sequentially (starting four weeks after the completion of chemotherapy). Subjects in the concurrent arm who achieve a complete response after four cycles of chemotherapy plus rituximab will receive additional rituximab alone once weekly for two more weeks. The study will compare the toxicity and effectiveness of the two regimens, as well as their effects on immune function (CD4 and CD8 cell count) and HIV and Epstein-Barr virus (EBV) viral loads. Finally, the study will look at whether concurrent use of rituximab or anti-HIV therapy alters the concentration of etoposide, doxorubicin, or vincristine in the body. Participants will be followed every three months for two years, then every six months for three years, then annually thereafter.

Eligible participants must be at least 18 years of age with confirmed, previously untreated stage II, III, or IV CD20+ B cell NHL. Various laboratory criteria must be met. Subjects are not eligible if they have acute OIs (except for *Mycobacterium avium* complex [MAC]) or other cancers besides lymphoma. Participants must be willing to use birth control, if appropriate, and women may not be pregnant or breast-feeding.

The study will be conducted at **San Francisco** General Hospital (415-206-8000) and the Albert Einstein Clinical Cancer Center in **New York City** (718-904-2783); *www.clinicaltrials.gov/ct/show/NCT00049036*. (CDR0000257660; AMC-034)

III) Finally, an NCI pilot study will look at treatment with EPOCH chemotherapy plus rituximab in HIV positive people with previously treated NHL. Eligible participants must be at least 18 years of age and have confirmed, aggressive CD20+ NHL (any stage). They must have been treated in the past with up to two chemotherapy regimens. Subjects will stop anti-HIV therapy during chemotherapy for NHL. Again, various laboratory criteria must be met, serious underlying medical conditions are excluded, and women may not be pregnant or breast-feeding.

This study will be conducted at the National Cancer Institute in **Bethesda** (888-624-1937), and enrolled participants will be reimbursed for travel to the study site; *www.clinicaltrials.gov/ct/show/NCT00001563*. (970040; 97-C-0040)

Human Papillomavirus in Women

This natural history study will attempt to determine whether use of antiretroviral therapy affects the incidence of human papillomavirus (HPV) infection in women with HIV. HPV is associated with cervical, genital, and anal dysplasia (abnormal cell growth) and cancer. Researchers hypothesize that as anti-HIV treatment improves immune system function, women may be less likely to contract HPV or may experience less aggressive HPV disease progression. At baseline, at weeks 24 and 48, and then every 48 weeks until

study completion, women will receive a pelvic exam and collection of cervical cell specimens using Pap smears and other methods. Those with abnormal Pap smear results will receive a colposcopy (a procedure in which the cervix is examined with a lighted magnifying instrument). Blood will be collected to monitor HIV viral load, CD4 cell counts, and the presence of HPV antibodies.

Participants must be at least 13 years of age and menstruating. They must intend to start antiretroviral treatment within 14 days of study entry, either as part of another clinical trial or under the care of their own physicians. Women are not eligible if they have previously received antiretroviral therapy for more than 14 days or if they are taking certain immune-modulating, anti-HPV, or experimental drugs. They may not have a history of cervical cancer and may not have participated in previous HPV trials.

There are 50 study sites, including **Atlanta** (404-616-6313), **Baltimore** (410-614-4487), **Birmingham** (205-975-7925), **Boston** (617-632-0785), **Chicago** (312-695-5012), **Cleveland** (216-778-5489), **Durham** (919-668-0161), **Los Angeles** (323-343-8283), **Miami** (305-243-2154), **New York City** (212-420-4432), **San Francisco** (415-514-0550 ext. 362), **San Juan, Puerto Rico** (787-759-9595), and **Washington, DC** (202-865-1248); *www.clinicaltrials.gov/ct/show/NCT00006444.* (ACTG A5029)

Postpartum HIV Disease Progression

The goal of this natural history study is to determine whether viral load increases in HIV positive women after they give birth, and if so, why. Some research to date appears to indicate that HIV levels increase postpartum (after childbirth) in some women. This may be due to changes in adherence to antiretroviral therapy during late pregnancy or following childbirth, pregnancy-related pharmacokinetic changes, or alterations in the immune system. Participants in this trial should be on stable HAART before delivery and continue taking it throughout the study. Regimens will be selected by the women's own physicians; no drugs are provided by this study. Participants will be evaluated at weeks 34 and 36 of gestation, at delivery, and then regularly for 96 weeks postpartum; viral load, CD4 cell count, and other laboratory values will be measured. A substudy (A5153s) will look at the pharmacokinetics of nelfinavir (Viracept) and lopinavir in HIV positive women during pregnancy and after childbirth.

Eligible women must be at least 13 years of age and between 22 and 30 weeks pregnant. They should be on stable HAART for at least eight weeks prior to delivery. Certain medications are excluded. Women in this study must agree not to breast-feed.

There are 14 study sites, including **Atlanta** (404-616-6313), **Birmingham** (205-975-7925), **Chicago** (312-942-5865), **Nashville** (615-467-0154 ext. 108), **Newark** (973-972-3118), **Providence** (401-793-4396), **San Diego** (619-543-8080), **San Francisco** (415-514-0550 ext. 354), and **San Juan, Puerto Rico** (787-765-4186); *www.clinicaltrials.gov/ct/show/NCT00041964.* (ACTG A5150)

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San Francisco AIDS Foundation Bilingual Hotline

(English/Spanish)

415-863-AIDS

Toll-Free in California

800-367-AIDS

The California AIDS Hotline volunteers provide support and confidential, comprehensive information about HIV transmission, test sites, prevention, and treatment in English and Spanish. A TDD line is also available for the hearing-impaired. The Hotline operates from 9:00 am to 5:00 pm Monday through Friday, and Tuesdays 9:00 am to 9:00 pm.

In California, call toll-free

800-367-2437

In San Francisco or out of state, call

415-863-2437

The TDD line in California is

888-225-2437

glossary

A

ACID-BASE BALANCE (pH):
the normal equilibrium between acids and bases in the body. Normally the blood is slightly alkaline, or basic.

ACTIVITY:
the immediate effect of a drug on a disease-causing microbe. Contrast with *efficacy.*

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

ADHERENCE:
following a prescribed treatment regimen, including correct dosages, number of doses per day, and dietary restrictions.

ANTIBIOTIC:
an agent that inhibits the growth of or destroys microorganisms; the term typically refers to an agent that is active against bacteria.

ANTIBODY (AB, IMMUNOGLOBULIN):
a protein secreted by activated plasma cells, which evolve from B cells. Antibodies are produced in response to stimulation by foreign antigens as part of the body's defense against invaders. Specific antibodies bind to and act upon specific antigens.

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

ANTIRETROVIRAL:
an agent (e.g., AZT, ritonavir, efavirenz) that suppresses the activity or replication of retroviruses such as HIV by interfering with various stages of the viral lifecycle.

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

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

ASYMPTOMATIC:
not showing outward signs of a disease.

B

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

BILE:
a substance produced by the liver that aids in the digestion of fats.

BONE MARROW:
the soft, spongy tissue in the interior of certain bones (e.g., the long bones of the limbs). Bone marrow contains stem cells and is the site of blood cell production.

C

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

CD4 CELL (CD4 LYMPHOCYTE, T-HELPER CELL):
a type of white blood cell that bears the CD4 cell surface receptor and helps the body fight infection. HIV attacks CD4 cells, typically resulting in their dysfunction or death.

CERVIX (*adjective* CERVICAL):
the cylindrical, lower part of the uterus leading into the vagina.

CHEMOTHERAPY (*adjective* CHEMOTHERAPEUTIC):
the use of chemicals or drugs to treat disease. The term is typically used to refer to cancer treatment.

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

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

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

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

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

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

CYTOTOXIC T LYMPHOCYTE (CTL, KILLER T CELL):
a type of white blood cell that bears the CD8 surface marker, and targets and kills infected or cancerous cells. The action of CTLs is coordinated by CD4 cells via the production of cytokines.

D

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

E

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

ELECTROLYTE:
an electrically charged molecule, or ion (e.g., sodium, potassium) found in body fluids, tissues, and cells. An imbalance of electrolytes can result from prolonged vomiting or diarrhea, and may lead to the disruption of many body processes, possibly resulting in muscle weakness, cramps, or seizures.

ERADICATION:
the complete elimination of an organism (e.g., HIV) from the body, including the blood and reservoir tissue sites.

G

GASTROINTESTINAL:
relating to the stomach and intestines.

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

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

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

H

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

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

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

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

I

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

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

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

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

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

IN VITRO:
Latin for "in glass." Refers to studies done in a test tube or culture medium in the laboratory.

L

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

LEUKEMIA:
a cancerous disease of the blood characterized by the proliferation of white blood cells.

LIPID:
a fat.

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

LYMPH NODE (LYMPH GLAND):
a small, bean-sized organ located throughout the body, with concentrations in the neck, groin, and armpits. Lymph nodes filter out antigens and are the site of antigen presentation and immune cell activation. The lymph nodes are a reservoir site for HIV.

LYMPHOMA:
cancer of the lymphoid tissue. Lymphoma may spread out of the lymph nodes (extranodal disease) and into the brain, bone marrow, or liver; primary central nervous system lymphoma originates in the brain. Symptoms include swollen lymph nodes, weight loss, and fever. Lymphomas are classified as Hodgkin's disease or non-Hodgkin's lymphoma (NHL); NHL is more common in people with HIV/AIDS.

M

MEAN:
the average of a set of values. Contrast with *median.*

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

METABOLISM (*adjective* METABOLIC):
the processes of building the body's molecular structures from nutrients and breaking them down for energy. Also, the chemical breakdown of drugs and toxins within the body.

MONOCLONAL ANTIBODY (MAB):
an antibody derived (often by genetic engineering) from a single clone of cells. MABs are specifically directed against a particular epitope (a unique marker on an antigen that can trigger an antibody response) and are used as tools to detect and identify specific proteins.

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

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

N

NATURAL KILLER CELL (NK CELL):
a type of white blood cell that attacks and kills tumor cells and cells infected with microorganisms. Unlike cytotoxic T lymphocytes, NK cells are nonspecific and attack infected cells without regard to specific antigens.

O

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

P

PANCREAS:
a digestive gland in the abdominal cavity. The pancreas is responsible for secreting digestive enzymes into the intestines. Small glands in the pancreas (the Islets of Langerhans) produce insulin.

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

PATHOGEN (*adjective* PATHOGENIC):
any disease-causing agent, especially a microorganism.

PERSON-YEAR (PATIENT-YEAR):
a shorthand term used by epidemiologists to make comparisons. Its value is determined by multiplying the number of persons by the number of years. For example, one person followed for ten years equals ten person-years, and ten persons followed for one year also equals ten person-years.

PHASE I TRIALS:
studies conducted in a small number of healthy (e.g., HIV negative) volunteers (typically 10–100); sometimes testing in people with the disease under study (e.g., HIV disease) may begin in Phase I. These early trials establish the pharmacokinetics of a drug (how it is absorbed, processed, and excreted by the body), its safety and tolerability, and the best doses.

PHASE II TRIALS:
trials that involve a larger number of participants with the disease under study (typically 50–500). While researchers continue to look for toxicities, they also seek preliminary indications of effectiveness, or efficacy. Sometimes Phase I and II or Phase II and III trials are combined to speed the development process.

PHASE III TRIALS:
studies that include the largest number of participants (typically hundreds or thousands). These trials are designed to determine whether a drug is effective. They also continue to monitor toxicity, especially longer-term side effects.

PHASE IV TRIALS:
postmarketing studies conducted after an agent has been approved. They are intended to further confirm efficacy and safety under "real world" conditions, and are especially valuable for detecting long-term and uncommon side effects that do not show up in Phase III trials.

PHENOTYPE (*adjective* PHENOTYPIC):
visible characteristics and/or behaviors that result from the interaction of an organism's genetic "blueprint" (genotype) and the environment. Phenotypic resistance testing determines whether an organism is susceptible to a specific drug in a test tube. Contrast with *genotype.*

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

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

PREVALENCE (PREVALENCE RATE):
the number of existing cases of a disease or condition in a specific population

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

PROGRESSION:
advancement or worsening of a disease.

S

STANDARD OF CARE:
the level of care that all people with a particular illness should receive, the level below which care would be considered substandard.

STEROID:
one of a family of substances that share a similar chemical structure, including certain hormones (e.g., testosterone) and various drugs. Some steroid drugs are used to diminish inflammatory reactions.

STRUCTURED TREATMENT INTERRUPTION (STI):
starting and stopping treatment on a specified, monitored schedule.

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

SYMPTOMATIC:
showing outward signs of a disease.

SYNERGY (SYNERGISM, *adjective* SYNERGISTIC):
an interaction between agents (e.g., drugs) that produces an effect greater than the combined effects of the same agents used separately.

T

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

TRIGLYCERIDE:
a combination of glycerol and fatty acid that circulates in the blood. Elevated triglyceride levels, particularly when accompanied by elevated levels of low-density lipoprotein (LDL) cholesterol, are associated with the development of cardiovascular disease.

V

VIRAL REBOUND (VIRAL BREAKTHROUGH):
an increase in viral load following a previous decrease due to anti-HIV therapy.

VIRAL TURNOVER:
the rate at which virus dies and is regenerated.

VIRUS:
any of a large group of minute organisms that cannot grow or reproduce outside a host cell.

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

- **National AIDS Hotline**
  (Monday–Friday,
  10:00 AM to 10:00 PM, Eastern Time)
  800-243-7889 TTY

- **National HIV/AIDS Treatment Information Service**
  (Monday–Friday,
  9:00 AM to 5:00 PM, Eastern Time)
  888-480-3739 TTY
  www.aidsinfo.nih.gov

- **Deaf AIDS Support Services (DASS) at the University of California, San Francisco (UCSF) Center on Deafness**
  415-476-7600 TTY
  uccd@itsa.ucsf.edu

- **Deaf AIDS Project (Baltimore, MD)**
  410-889-8077 TTY
  www.deafvision.net/dap

- **AIDS Initiative for Deaf Services Task Force (Hartford, CT)**
  860-951-4791 TTY
  www.aidsprojecthartford.org/deafaidsct.html

Have You Moved?

Please affix a mailing label if possible, or print your **OLD** address below:

Name

Address

City State Zip

Please print your **NEW** address below:

Name

Address

City State Zip

Send this form to: *BETA*, PO Box 426182, San Francisco, CA 94142-6182

Yes, I'd like to support *BETA*

and other HIV/AIDS services at the San Francisco AIDS Foundation

❒ $100 ❒ $75 ❒ $50 ❒ $_____

Name

Address

City State Zip

❒ My check is enclosed

I prefer to donate with my credit card ❒ AMEX ❒ VISA ❒ MasterCard ❒ Discover

Card number: Expiration date:

Send this form to:
San Francisco AIDS Foundation, File 72635, PO Box 60000, San Francisco, CA 94160-2635

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