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# BETA

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*Nutrition and HIV*

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*Interpreting  
Medical Research*



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WINTER 2006

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

*In the summer and fall of 2005, a number of conferences throughout the world presented HIV-related findings. Other HIV news during this time is also reported here.*

Several recent medical conferences featured reports related to HIV/AIDS, including the XIV International HIV Drug Resistance Workshop, held June 7–11 in Quebec; the 3<sup>rd</sup> International AIDS Society (IAS) Conference on HIV Pathogenesis and Treatment, held July 24–27 in Rio de Janeiro; the 7<sup>th</sup> International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, November 13–16 in Dublin; the 10<sup>th</sup> European AIDS Clinical Society (EACS) annual meeting, also in Dublin, November 17–20; and the 1<sup>st</sup> International Workshop on Targeting HIV Entry, held December 2–3 in Bethesda, Maryland. The 45<sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) took place December 16–19 in Washington, DC; ICAAC usually occurs earlier in the fall, but this year was postponed and relocated after Hurricane Katrina struck New Orleans a few weeks before the originally scheduled date. In addition, the 56<sup>th</sup> Annual Meeting of the American Association for the Study of Liver Disease (AASLD), held November 11–15 in San Francisco, included several presentations on HIV/hepatitis C coinfection.

Highlights from these conferences are included below, organized by topic. Due to the amount of information presented at these meetings, *BETA*'s news summary is necessarily incomplete; for more in-depth reports, see the websites below.

**O N T H E W E B****INTERNATIONAL AIDS SOCIETY CONFERENCE (IAS):**

[www.ias-2005.org](http://www.ias-2005.org)

**EUROPEAN AIDS CLINICAL SOCIETY (EACS):**

[www.eacs-conference2005.com](http://www.eacs-conference2005.com)

**INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY (ICAAC):**

[www.icaac.org/45ICAAC](http://www.icaac.org/45ICAAC)

**AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASE (AASLD):**

[www.aasld.org](http://www.aasld.org)

**CONFERENCE COVERAGE**

[www.aidsmap.org](http://www.aidsmap.org)

[www.hivandhepatitis.com](http://www.hivandhepatitis.com)

[www.natap.org](http://www.natap.org)

[www.thebody.com](http://www.thebody.com)

**NEW KALETRA FORMULATION APPROVED**

On October 28, the Food and Drug Administration (FDA) approved a new formulation of Kaletra (lopinavir/ritonavir combination pill) that allows patients to take four instead of six pills per day. Each new film-coated “Meltrex” tablet contains 200 mg lopinavir and 50 mg ritonavir. Last April, the agency approved a once-daily Kaletra dosing regimen for some treatment-naïve individuals: four of the new tablets once daily, for a total dose of 800 mg lopinavir and 200 mg ritonavir. The dosage remains two tablets twice daily for treatment-experienced patients. The new tablet does not require refrigeration and can be taken on a full or empty stomach (the old soft-gel capsule had to be taken with food). As reported at the IAS meeting, bioavailability of the new formulation is less affected by food (*abstract WeOa0206*). Studies presented at ICAAC showed that the new pill was 17% more bioavailable, caused fewer gastrointestinal side effects (especially diarrhea), and promoted better adherence over 96 weeks compared with the old formulation (*abstracts H-1894 and H-522*). The new tablet will cost about 8% more, and Abbott Laboratories has requested an extension of its patent on the drug (due to expire in 2015). For complete prescribing information, see [www.kaletra.com](http://www.kaletra.com).

**AVOID AMEVIVE**

People with HIV should avoid the psoriasis drug alefacept (Amevive) since it can reduce CD4 cell counts, the FDA and the drug's manufacturer, Biogen Idec, recently cautioned. In October, Biogen sent a letter to this effect to healthcare providers, warning that the medication “might accelerate disease progression or increase complications of disease” in people with HIV/AIDS.

**UPDATED HIV TREATMENT GUIDELINES**

Also in October, the U.S. Department of Health and Human Services (DHHS) released an updated version of its “Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.” Based on recent worrisome clinical trial data, the new guidelines recommend against regimens that combine dDI (didanosine, Videx)

**September 17 marked a milestone in the AIDS epidemic: the first expiration of a patent on an antiretroviral drug.**

plus tenofovir DF (Viread) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI), due to reports of early virological failure and rapid emergence of NNRTI resistance. The new guidelines also provide information about the new protease inhibitor (PI) tipranavir (Aptivus) and a revised section on medical management of treatment-experienced patients. The new, more aggressive goal in treating this group is to suppress HIV to undetectable levels—not merely to preserve immune function and delay disease progression—which may be accomplished (even in patients with multidrug-resistant HIV) using a boosted PI plus T-20 (enfuvirtide, Fuzeon). DHHS also recently updated its pediatric HIV treatment guidelines. For the latest updated guidelines for HIV treatment in adults, adolescents, children, and pregnant women; post-exposure prophylaxis (PEP) for occupational and nonoccupational exposure; and opportunistic illness (OI) prevention, see [www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov).

### **NPs, PAs, AND MDs PROVIDE SIMILAR QUALITY CARE**

As the guidelines for antiretroviral therapy grow ever more complex, it becomes increasingly challenging for medical practitioners to keep abreast of the latest developments. But according to a study published in the November 15, 2005 *Annals of Internal Medicine*, quality of HIV care is not dependent on type of medical degree. Looking at more than 6,600 patient records from 68 Ryan White CARE Act-funded HIV clinics, Ira Wilson, MD, from Tufts University and colleagues analyzed eight quality of care factors including use of HAART and preventive screenings (e.g., for hepatitis C, cervical cancer, and tuberculosis). They found that nurse practitioners (NPs) and physician assistants (PAs) provided a comparable level of care to physicians (medical doctors or MDs) specializing in HIV/AIDS, and generally performed better than non-specialist general practitioner MDs. Both NPs and PAs—but not registered nurses, or RNs—are trained in how to diagnose patients and select medications (though MDs usually must authorize their prescriptions). The best NP and PA care was delivered by providers who specialize in HIV/AIDS, have practical experience in this field, and work closely with HIV specialist physicians. These results are reassuring for managed care and HMO patients—as well as those in rural or otherwise underserved areas—who may have more ready access to NPs or PAs than to MDs.

### **FIRST ANTI-HIV DRUG GOES OFF PATENT**

September 17 marked a milestone in the AIDS epidemic: the first expiration of a patent on an antiretroviral drug. In March 1987, GlaxoSmithKline's AZT (zidovudine, Retrovir) was the first drug approved for the treatment of

HIV/AIDS; it was initially used as monotherapy which, as soon became apparent, encouraged the rapid development of drug-resistant virus. Today, AZT remains a standard component of HAART “backbone” regimens, though its popularity has faded due to toxicity concerns and more patient-friendly alternatives. The drug is also included in two fixed-dose combination pills, Combivir (AZT/3TC) and Trizivir (AZT/3TC/abacavir). Since its approval, AZT has generated about \$4 billion in sales. While AZT alone no longer commands a large market share, Combivir is among the top-selling anti-HIV therapies. The recent patent expiration applies only to AZT itself, not the combination pills. Just days after the patent expired, the FDA approved four generic versions of AZT, produced by three different companies (Aurobindo, Ranbaxy, and Roxane Laboratories) for sale in the United States. Generic versions are expected to cost less than \$100 per year, compared with nearly \$4,000 annually (wholesale) for brand-name Retrovir. Generic versions of AZT and fixed-dose combination pills containing the drug were already manufactured by several overseas companies, either licensed by Glaxo or produced under World Trade Organization provisions for developing countries with health emergencies.

### **UNUSUAL NEW YORK HIV CASE AN ANOMALY**

The Summer 2005 issue of *BETA* included a news item about a gay man in New York City with an unusual multi-drug-resistant, dual-tropic (able to use both CCR5 and CXCR4 coreceptors to enter cells) strain of HIV with a high capacity for replication; the case was described in detail in the March 19, 2005 issue of *The Lancet*. The report prompted a flurry of media attention last winter, as well as much discussion—some of it acrimonious—among medical professionals and HIV prevention workers. Several medical experts and community advocates criticized New York public health officials and researchers at the Aaron Diamond AIDS Research Center (where the case was discovered) for raising the alarm prematurely based on a single patient.

The case prompted a rare special symposium at the February 2005 Conference on Retroviruses and Opportunistic Infections and it was discussed again at the July IAS meeting. While some raised concern that the case might be a harbinger of a new, more aggressive HIV “superstrain,” those fears now seem unwarranted, as the New York case appears to be an anomaly. After extensive contact tracing and analysis of stored blood samples, it was determined that the Connecticut man who apparently transmitted HIV to the New York patient is himself experiencing a typical rate of HIV progression, although he also has multidrug-resistant virus. The Connecticut man's physician, Gary Blick, MD, and others have suggested that the aggressive

course of disease seen in the New York man might be due to individual genetic factors and/or his heavy use of crystal methamphetamine.

### **BRITISH MAN'S "CURE" QUESTIONABLE**

Just as the hype surrounding the New York "super-strain" later proved unfounded, the recent excitement over a British man's reported HIV "cure" appears equally unjustified. This past November, Andrew Stimpson gave interviews to two U.K. newspapers, the *News of the World* and *Mail on Sunday*, suggesting he cured his HIV with vitamin supplements. Stimpson said that in 2003 and 2004 he received multiple negative HIV antibody tests and undetectable viral load tests, after previously receiving one indeterminate and two positive antibody tests, as well as a very low but detectable viral load test, in 2002. After receiving the positive results, Stimpson reported, he began having unprotected sex with his HIV positive partner.

People truly infected with HIV may have viral loads below the limit of detection of a specific test (typically 50 copies/mL), but it would be unusual for an infected person to have both undetectable viral load and a negative antibody test. While "seroreversion" from HIV positive to HIV negative is rare, it has been observed in a few individuals treated early with antiretroviral therapy during acute infection (as reported in the March 5, 2005 issue of *Clinical Infectious Diseases [CID]*) and in some children who acquired HIV through mother-to-child transmission (as reported in a letter in the December 15, 2005 issue of *CID*); Stimpson, however, says he never received anti-HIV treatment.

Stimpson sued the Chelsea and Westminster Health Trust, alleging that its sexual health clinic must have mixed up his and another person's blood samples. The British National Health Service Litigation Authority confirmed that all tests were done using Stimpson's blood, but asked him to undergo further testing—a request he declined. Even if the blood samples were not mixed up, false-positive results could have resulted from laboratory errors, problems with the tests, or unusual viral or host factors that have yet to be determined.

### **RAPID ORAL HIV TEST GIVES FALSE-POSITIVE RESULTS**

In December, several U.S. agencies stopped using the OraQuick Advance rapid oral HIV antibody test after unexpectedly large numbers of false-positive results were reported at certain sites in a few cities; however, most agencies nationwide have not seen similar clusters of false-positives. The test, which uses a sample of oral fluid taken from around the gums, was approved in March 2004. According to the test manufacturer, OraSure Technologies, there were 107 false-positive results out of more than

28,400 tests conducted between January and November 2005, for a specificity rate of 99.6%. But in San Francisco, there were 49 false-positives out of about 9,400 tests performed that year. The New York City health department reported 30 false-positives in November alone, while the Los Angeles Gay and Lesbian Center reported 13. Similar problems have not been seen with OraSure's rapid finger-stick blood test. On December 16, the Centers for Disease Control and Prevention (CDC) issued an advisory stating that positive rapid oral HIV test results should always be confirmed using a supplemental test such as a Western blot or immunofluorescent assay. OraSure, CDC, FDA, and local health officials are investigating the cause of the erroneous results. Program directors can call 800-672-7873 to report further problems. Despite the recent spate of false-positives, many public health experts believe the rapid oral HIV test remains useful because it allows individuals to avoid needlesticks and to receive their results in 20 minutes, rather than having to return after 1–2 weeks.

### **IS HIV BECOMING WEAKER?**

According to a report by Belgian researchers in the October 14 issue of *AIDS*, HIV may be getting progressively weaker. Kevin Ariën and colleagues analyzed HIV-1 isolates from 24 treatment-naïve individuals, half of which were collected during the 1986–1989 period and half during 2002–2003; isolates were matched for subtype and coreceptor tropism (use of the CCR5 or CXCR4 coreceptors). The researchers found that the earlier isolates were more effective at entering and killing CD4 cells compared with the more recent strains. In 176 out of 238 head-to-head tests, the older isolate infected cells more readily than the newer one. Ariën's team calculated that the more recent virus isolates had a replicative fitness about 55% of that seen in the older isolates. They noted that this reduction in fitness may be a consequence of mutations the virus must undergo to evade the human immune response. In addition, pathogens commonly evolve to become less virulent over time, since they have more opportunities to replicate—and to be transmitted to new bodies—if they do not kill their hosts too quickly. These data suggest that the gains in health and longevity among people with HIV/AIDS over the past two decades may be due in part to weaker virus, in addition to the development of better antiretroviral therapies.

### **RECENT STUDIES EXPLORE HIV PROGRESSION**

Several recent studies have focused on HIV disease progression. At the ICAAC meeting (*abstract H-515*) and in the January 1, 2006 issue of *CID*, Nicolai Lohse and colleagues from Denmark reported that short-term virological

**The SMART study discontinued enrollment in January after data showed that continuous HAART is superior to episodic treatment guided by CD4 cell counts.**

suppression after starting a course of HAART is associated with long-term HIV suppression and survival. They analyzed data from 2,046 HIV positive subjects divided into three groups: those with continuous viral suppression (viral load below 400 copies/mL), those whose HIV was suppressed some of the time, and those who never had undetectable virus during the 6–18 months after HAART initiation. Subjects in the 100% suppression group were more likely to be alive after 72 months than those in the 1%–99% suppression group or the no suppression group (survival rates of 92.7%, 85.6%, and 76.1%, respectively), and were more likely to have undetectable viral load at the end of follow-up (96%, 83%, and 57%, respectively). They were also less likely to die of AIDS-related causes and had slightly larger CD4 cell count increases. However, compared with the 100% suppressed subjects, patients in the 1%–99% suppression and no suppression groups were more likely to be injection drug users, had lower pretreatment CD4 cell counts, were more likely to have previously tried antiretroviral therapy (especially suboptimal pre-HAART therapy), and had more prior treatment interruptions—all factors linked to worse outcomes. Thus, while the data indicate that viral breakthrough during early treatment predicts disease progression, they do not explain why. The negative outcomes seen in this study may, for example, be due to prior treatment history and resulting resistance, rather than early virological breakthrough *per se*.

In another recent study, primary drug resistance did not predict worse overall outcomes. As reported in the January 2, 2006 issue of *AIDS*, researchers with the international CASCADE Virology Collaboration analyzed 300 treatment-naïve individuals who received drug-resistance tests within 18 months after HIV infection; 10% (29 subjects) showed evidence of intermediate or high-level resistance to at least one antiretroviral agent. They found that patients initially infected with HIV that had one or more drug-resistance mutations did not progress more rapidly over five years. While patients with primary drug resistance experienced greater CD4 cell declines during the first year after infection than subjects infected with non-resistant HIV, both groups had similar CD4 cell counts after five years. In addition, primary drug resistance did not appear to impair response to first-line treatment. The authors concluded that the study provided no evidence of a long-term effect of transmitted drug resistance on the natural history of HIV disease, but cautioned that the negative impact of primary resistance may emerge even later in the course of disease if salvage therapy should become necessary.

These findings, if confirmed, are welcome news, since the prevalence of primary drug resistance appears to be on the rise, according to a report in the December 15, 2005

*Journal of Acquired Immune Deficiency Syndromes (JAIDS)*. Looking at data from the CASCADE cohort, Bernard Masquelier, PharmD, and colleagues reported that 45 out of 438 of patients (10.3%) who seroconverted between 1987 and 2003 were infected with drug-resistant strains of HIV. The prevalence of resistance was higher among men who have sex with men (11.6%) than among injection drug users (6.7%) or individuals infected through heterosexual contact (5.6%). The overall resistance rate increased between 1996–1999 and 2000–2003, leading the authors to conclude that transmitted drug resistance is rising over time and to emphasize the importance of developing new antiretroviral agents and novel drug classes.

### **SMART STUDY CANCELLED**

The SMART (Strategies for Management of Anti-Retroviral Therapy) study, a large international trial comparing two HIV treatment strategies, discontinued enrollment in January after data showed that continuous HAART is superior to episodic treatment guided by CD4 cell counts; in the United States, the trial was conducted by the Community Programs for Clinical Research on AIDS (CPCRA). The study, begun in 2002, was designed to determine whether patients at low risk of HIV disease progression could safely reduce their use of antiretroviral therapy in the hope of minimizing side effects, slowing the development of drug resistance, and preserving future treatment options. Participants—nearly 5,500 to date—were randomly assigned to either continue (or start) treatment in an attempt to keep their viral loads as low as possible, regardless of CD4 cell count (the viral suppression arm), or to stop anti-HIV therapy (or not start) until their CD4 cell counts fell below 250 cells/mm<sup>3</sup> (the drug conservation arm).

An independent Data and Safety Monitoring Board halted enrollment because patients in the drug conservation group had twice the risk of progression to AIDS or death after an average follow-up period of about 15 months. Subjects in that arm also had a higher incidence of cardiovascular, kidney, and liver problems—contrary to the hypothesis that episodic therapy might reduce the rate of adverse events. “We were surprised to learn that in the short term, episodic antiretroviral therapy carries such an increased risk without evidence of sparing patients the known side effects associated with [antiretroviral therapy],” said Wafaa El-Sadr, MD, one of the study’s principal investigators. After reviewing the data, the committee overseeing the trial recommended that treatment-experienced subjects currently in the drug conservation arm should restart HAART; follow-up will continue for all currently enrolled participants.

## DO SOME GROUPS BENEFIT MORE FROM TREATMENT?

According to a study published in the November 18, 2005 issue of *AIDS*, some people seem to benefit more from anti-HIV therapy than others. Caroline Sabin and colleagues with the Antiretroviral Therapy Cohort Collaboration analyzed changing patterns of HIV/AIDS morbidity and mortality as antiretroviral therapy evolved. Looking at data from more than 22,000 patients, they found that the rate of new AIDS-defining illnesses declined more steeply among gay men compared with other risk groups. While the incidence of AIDS-related events decreased overall after starting HAART, the reduction was not the same across all populations. During the first year of treatment, the researchers recorded 1,521 AIDS-defining events and 414 deaths, with the vast majority occurring during the first six months. Between the first and the second six-month periods, the combined event rate fell by 68%, from 12 to 4 per 100 person-years (PY). Among gay men, however, the decrease was 77%, compared with 59% among injection drug users. Patients who were already diagnosed with AIDS and those who had CD4 cell counts below 350 cells/mm<sup>3</sup> or viral loads above 100,000 copies/mL when they started antiretroviral therapy derived less benefit, as did those who started treatment after 2001.

But, according to researchers in Amsterdam, women using antiretroviral therapy appear to benefit as much as men. As reported in the March 4, 2005 issue of *AIDS*, Maria Prins, PhD, and colleagues conducted a review of the medical literature on sex differences in the rate of HIV disease progression before and after the advent of HAART. They found little evidence for sex differences in the rate of progression or the beneficial effects of anti-HIV therapy, even though some studies showed women were more likely to experience adverse side effects. Pregnancy also did not seem to worsen HIV disease progression. Given the complex effects of metabolic and hormonal factors, the authors emphasized the importance of including an adequate number of women in clinical trials of experimental anti-HIV therapies.

A related study found that among U.S. women, the benefits of antiretroviral therapy are not directly impacted by race/ethnicity. As reported in the August 15, 2005 issue of *JAIDS*, Kathryn Anastos, MD, and colleagues analyzed prospective data from 961 HIV positive women in the Women's Interagency HIV Study (WIHS) who started HAART between July 1995 and September 2003. After a median five years of follow-up, survival rates were 80% for white women, 77% for Hispanic/Latino women, and 70% for African-American women. While white women on the whole were more likely to achieve and maintain

virological suppression and less likely to die, these differences disappeared after adjusting for factors such as use of antiretroviral therapy, treatment discontinuation, pre-treatment CD4 cell count and HIV viral load, route of HIV exposure, history of AIDS-defining illnesses, use of illegal drugs, and depression. But the likelihood of treatment response was not related to genetic differences between racial/ethnic groups. Although African-American and Hispanic/Latino women were more likely to discontinue treatment and suffer from depression, the researchers concluded that “[n]o significant differences by race were found in virologic, immunologic, or clinical outcomes after adjustment for continued HAART use and depression.” They added that treatment of depression and strategies to promote continued use of antiretroviral therapy—including management of side effects—might lessen the apparent racial disparities observed in some studies.

## HAART CUTS HOSPITALIZATIONS AND DEATHS

It is widely recognized that the advent of effective combination therapy in the mid-1990s dramatically reduced the rate of AIDS-related deaths. Now, a new study has shown that HAART has reduced HIV-related hospitalizations in the United States by more than 50%. According to a report from the DHHS Agency for Healthcare Research and Quality (AHRQ), HIV-related hospital admissions fell from a high of 149,000 in 1995 to a low of 70,000 in 2003. The rate of AIDS-related mortality in U.S. hospitals also decreased from 12.5% to 8.5% during this period—a 32% decline. According to AHRQ director Carolyn Clancy, MD, “This information clearly highlights the benefits of quickly putting new, potentially life-saving medical advances into everyday clinical practice.” Another analysis by Jonathan Sterne, PhD, and colleagues, published in the July 30, 2005 issue of *The Lancet*, found that the use of HAART reduced the risk of progression to AIDS or death among the more than 3,200 participants in the Swiss HIV Cohort by 86%, compared with HIV positive individuals who did not receive antiretroviral treatment.

At the November EACS meeting, Charlotte Lewden and colleagues reported that the rate of death among patients who maintain high CD4 cell counts on therapy was similar to that seen in the HIV negative population as a whole (*abstract PE18.4/8*). In the French APROCO and Aquitaine cohorts, 24% of the nearly 2,280 participants were “favorable responders,” with CD4 counts higher than 500 cells/mm<sup>3</sup> and viral loads below 10,000 copies/mL while on HAART. The death rate in this subgroup was 0.7%—not significantly greater than the rate for age- and sex-matched individuals in the general population.

**While antiretroviral therapy may increase the risk of liver dysfunction and metabolic problems, the profound decrease in hospitalization and death rates since the mid-1990s indicates that, on the whole, the benefits of HAART have outweighed the risks.**

Unsurprisingly, patients with CD4 counts under 200 cells/mm<sup>3</sup> were nearly 24 times more likely to die. But even those with CD4 counts of 200–350 cells/mm<sup>3</sup> or 350–500 cells/mm<sup>3</sup> had mortality rates nearly five times and about three times higher, respectively, than those with more than 500 cells/mm<sup>3</sup>. Other factors that influenced mortality were sex (with women having a greater risk of death than men), injection drug use, and coinfection with hepatitis C.

Another change in the epidemic is the manner in which HIV causes illness and death. In the early years of the epidemic, most HIV positive patients were hospitalized or died due to opportunistic illnesses (OIs). While AIDS-related illnesses are still a major cause of morbidity and mortality, as HIV positive people receiving HAART live longer, they become more prone to chronic conditions associated with aging, as well as to diseases (such as chronic viral hepatitis) that progress over long periods. As reported in the December 15, 2005 issue of *JAIDS*, Kelly Gebo, MD, and colleagues conducted a cross-sectional analysis of approximately 317,000 HIV-related hospital admissions in 12 states in 1996, 1998, and 2000. They found that total admissions decreased by more than 30%, from 129,000 to 92,000; the decline was less pronounced among women and African-Americans. There were twice as many admissions for OIs in 1996 compared with 2000 (51,000 vs 25,000, or 40% vs 27%, respectively) and the number of admissions related to injection drug use remained stable at about 6% (6,400 vs 5,200). Liver-related admissions rose from 8% in 1996 to 13% in 2000 (10,500 vs 11,500), with the percentage due to hepatitis C increasing from 1% to 5%. Also on the rise were admissions due to cardiovascular disease (462 vs 800) and diabetes (4,000 vs 4,500). Looking more closely at liver-related deaths among the nearly 12,000 participants in the EuroSIDA cohort, Amanda Mocroft, MD, and colleagues reported in the December 2, 2005 issue of *AIDS* that the rate of death due to liver disease increased 13% from the pre-1995 to the post-2004 period after adjusting for CD4 cell count. The authors attributed the increase to a longer period of progression of chronic viral hepatitis B and C, liver toxicity due to antiretroviral drugs, and perhaps other unknown factors as well.

While antiretroviral therapy may increase the risk of liver dysfunction and metabolic problems, the profound decrease in hospitalization and death rates since the mid-1990s indicates that, on the whole, the benefits of HAART have outweighed the risks.

## TRUVADA VERSUS COMBIVIR

Recent data suggest that Gilead's once-daily fixed-dose combination pill, Truvada (tenofovir/emtricitabine), may

work better than GlaxoSmithKline's Combivir (AZT/3TC) when used as a nucleoside reverse transcriptase inhibitor (NRTI) background regimen. In the open-label Gilead 934 study (presented at the IAS meeting [*abstract WeOa0202*] and published in the January 19, 2006 *New England Journal of Medicine*), 517 treatment-naïve subjects were randomly assigned to receive either once daily tenofovir/emtricitabine or twice-daily Combivir, both in combination with once-daily efavirenz (Sustiva). After 48 weeks, 80% of patients in the tenofovir/emtricitabine arm achieved viral loads below 50 copies/mL, compared with 70% in the AZT/3TC arm. While the virological failure rates were very similar—and very low—for both regimens, tenofovir/emtricitabine was better tolerated; discontinuation rates due to adverse events were 4% in that arm, compared with 9% in the Combivir arm. The researchers concluded that tenofovir/emtricitabine “proved superior in terms of virologic suppression, CD4 response, and adverse events resulting in discontinuation of the study drugs.” In a January 18 press release, however, Glaxo countered that Combivir has a better long-term safety and efficacy record, having been evaluated in more than 50 randomized clinical trials involving more than 18,000 subjects. The company added that a higher than usual rate of anemia in the Combivir arm contributed to the difference in treatment failure rates seen in the 934 study.

Data from the COMET study presented at ICAAC offered evidence that the Truvada combination pill works at least as well as the separate tenofovir and emtricitabine pills used together. This Phase IV (postmarketing) trial included 411 subjects, about half of whom reached the 24-week analysis point, who switched from Combivir to Truvada while continuing efavirenz. While 59% of participants had viral loads below 50 copies/mL before the switch, that figure increased to 76% by week 24. Regimens taken less often and those containing fewer pills have been shown to improve adherence, which may have contributed to improved virological suppression in this study; 85% of subjects said they made the switch from Combivir to Truvada for the convenience of a complete once-daily regimen (*abstract H-517*).

While Truvada looks like a win for Gilead, the company has struggled in its joint effort with Bristol-Myers Squibb to combine tenofovir, emtricitabine, and efavirenz into a single three-way combination pill. In April and August 2005, the companies announced that their first two such attempts had failed: the candidate combination pills were not bioequivalent to the three separate drugs used together. In January, however, the companies issued a joint statement that another co-formulation using bi-layer technology did appear to produce blood levels equivalent to those seen with the separate drugs. Gilead and Bristol-Myers

While the demise of two CCR5 inhibitor candidates is disappointing, it does not mean the entire class is doomed.

Squibb said they plan to file an Investigational New Drug application with the FDA in the second quarter of 2006. If the effort is successful, it will be the first ever complete one-pill, once-daily antiretroviral regimen; this is also the first cross-company collaboration to develop a fixed-dose combination pill consisting of drugs patented by different manufacturers.

## ONE CCR5 ANTAGONIST PRAISED, TWO BURIED

CCR5 antagonists, a novel class of HIV entry inhibitors, have featured prominently in recent drug development news. Most strains of HIV use the CCR5 coreceptor to enter cells, and blocking this receptor can interrupt viral replication. At the IAS meeting, Mary McHale from Pfizer reviewed six studies of the company's experimental CCR5 antagonist, **maraviroc** (UK-427, 857), involving a total of 259 HIV negative volunteers and HIV positive patients. In two Phase I/IIa monotherapy studies with 63 subjects, maraviroc reduced HIV viral load by 1.60–1.84 logs after 10 days; the 300 mg dose was selected for further development (*abstract TuOa0204*). At the June drug resistance workshop, researchers presented *in vitro* data showing that HIV that developed resistance to maraviroc remained sensitive to other candidate CCR5 inhibitors. In studies to date, maraviroc appeared well tolerated at doses up to 300 mg twice daily, with adverse events similar to those seen in placebo arms (e.g., headache, nausea, flatulence). The FDA has granted the drug "fast track" status since it potentially fills an unmet need for treatment-experienced patients who have exhausted currently available therapeutic options. Phase IIb/III trials in both treatment-naïve and treatment-experienced individuals are currently enrolling (see "Open Clinical Trials" on page 49).

Researchers at IAS also presented data on Schering-Plough's CCR5 inhibitor candidate, **vicriviroc** (SCH-D or SCH 417690). D. Schuermann and colleagues conducted a randomized, dose-ranging study in which 48 HIV positive subjects were randomly assigned to receive one of three doses of vicriviroc or placebo. After 14 days, the mean reduction in HIV viral load was 1.62 logs in subjects receiving the 50 mg dose. Vicriviroc was generally well tolerated in doses up to 100 mg daily, but a few patients experienced seizures and some developed transient liver enzyme elevations (*abstract TuOa0205*). Schering researchers reported at ICAAC that vicriviroc exhibited potent antiviral activity against drug-resistant HIV and that no more clinically relevant heart rhythm disturbances were observed than with placebo (*abstracts H-1096 and H-1095*). The company, however, announced in October that it was halting Phase II trials of vicriviroc in treatment-naïve subjects

due to early virological breakthrough. After several weeks of therapy, study participants receiving vicriviroc plus AZT/3TC were more likely to experience viral load rebound than subjects taking efavirenz plus AZT/3TC. A study of the drug in treatment-experienced individuals is ongoing, and the company said it would continue to evaluate the potential use of vicriviroc in combination with other treatment regimens.

Schering's announcement came just two days after GlaxoSmithKline announced that it was stopping all trials of its CCR5 candidate, **aplaviroc** (GSK-873,140), because some study participants developed serious liver toxicity. The company first halted a Phase IIb trial in treatment-naïve individuals in September, after two subjects (out of about 250) developed severe liver enzyme elevations. On October 25, a Phase III study in treatment-experienced patients (just started in July, with about 50 enrollees) was also stopped for the same reason. Glaxo's Helen Steele discussed these toxicity cases—plus a fourth—at the EACS conference. She said all four patients had alanine aminotransferase (ALT, a liver enzyme) levels more than three times the upper limit of normal—70 times in one case—plus transiently elevated bilirubin. While these patients all recovered after the drug was discontinued, this type of complication is potentially life-threatening. According to the company, "No further clinical studies of the compound are planned at this time."

While the demise of two CCR5 inhibitor candidates is disappointing, it does not mean the entire class is doomed. Schering said its decision to abandon vicriviroc was not related to liver toxicity or other significant safety issues. In July and September, an independent Data Safety Monitoring Board (DSMB) reviewed the safety data on maraviroc, concluding that trials should continue without major design changes. But at the EACS meeting two months later, a Pfizer representative announced that the company had recently learned of a single case of severe liver toxicity in an individual taking the drug in a clinical trial. Pfizer's Howard Mayer, MD, reviewed the case at the Targeting HIV Entry workshop in December. The treatment-naïve patient—who was coinfecting with hepatitis C and had pre-existing liver damage—began to experience rising liver enzyme levels during the pretreatment study screening period. He developed a fever and skin rash after taking four doses of maraviroc plus Combivir. His ALT level continued to rise after maraviroc was replaced with lopinavir/ritonavir, ultimately necessitating a liver transplant. The patient was also taking acetaminophen, isoniazid, and trimethoprim/sulfamethoxazole (TMP/SMX), any of which may have contributed to his liver toxicity. The DSMB suggested that the other medications were more

**TMC114 (now named darunavir), a novel nonpeptide PI, is among the most promising experimental agents moving along the development pipeline.**

likely the cause of liver injury, but maraviroc's role could not be ruled out. They recommended that trials continue, but use of isoniazid has been added as an exclusion criterion. Anyone currently enrolled in clinical trials of maraviroc (or any other CCR5 antagonist) should undergo careful liver function monitoring.

The FDA has scheduled an open public meeting to discuss development of CCR5 antagonists in February or March 2006 and is currently seeking public input from the patient and advocacy communities and from researchers. For more information, see [www.hivforum.org/CCR5](http://www.hivforum.org/CCR5).

### TMC114 LOOKS POWERFUL

TMC114 (now named darunavir), a novel nonpeptide PI, is among the most promising experimental agents moving along the development pipeline. At the IAS meeting, Christine Katlama, MD, presented data from a multicenter Phase IIb trial (POWER 1) in which 318 treatment-experienced individuals with resistance to other PIs were randomly assigned to receive one of four doses of ritonavir-boosted TMC114 or a currently approved PI, all with an optimized "backbone" of two NRTIs and possibly T-20 (*abstract WeOaLB0102*). After 24 weeks, 53% of patients in the arm taking 600/100 mg TMC114/ritonavir twice daily (the most effective dose) achieved HIV viral loads below 50 copies/mL, compared with 18% of subjects taking other PIs; 77% and 25%, respectively, experienced at least a 1 log drop in HIV RNA. The corresponding mean CD4 cell increases were 124 and 20 cells/mm<sup>3</sup>. Katlama and colleagues concluded that TMC114/ritonavir "demonstrated unprecedented efficacy" in treatment-experienced patients with limited therapeutic options." TMC114 was well tolerated overall, according to a safety analysis by Beatriz Grinsztejn, MD, and colleagues (*abstract WePeLB6.2C01*); just 10% of subjects discontinued TMC114 prematurely, compared with 62% in the control arm, mostly due to virological failure.

Timothy Wilkin, MD, presented data from the companion POWER 2 study at ICAAC (*abstract H-413*). In this trial, 62% of treatment-experienced subjects with PI-resistance mutations receiving 600/100 mg TMC114/ritonavir achieved at least a 1 log viral load decrease at 24 weeks, compared with 14% in the comparator PI arm; percentages achieving undetectable viral loads were 39% and 7%, respectively. Adverse event rates were similar across all arms.

Based on the results of these two studies, Tibotec Pharmaceuticals submitted a new drug application to the FDA on December 27. A Phase III clinical trial of TMC114 in treatment-naïve individuals is currently enrolling, and in October Tibotec announced an expanded access program for treatment-experienced patients with advanced HIV

disease who are ineligible for ongoing trials (see "Open Clinical Trials" on page 48).

### NEW DRUGS IN EXISTING CLASSES

Preliminary data on another new PI, **brecanavir** (GW640385 or VX-385, jointly developed by GlaxoSmithKline and Vertex) were presented at ICAAC by Douglas Ward, MD (*abstract H-412*). Like other nonpeptide PIs, brecanavir binds tightly to HIV's protease enzyme and demonstrated activity against virus resistant to conventional PIs. In this open-label study, 31 subjects (six of them treatment-experienced with resistant virus) received 300 mg brecanavir twice daily boosted with 100 mg ritonavir, plus two NRTIs (excluding tenofovir). At 24 weeks, 81% achieved viral loads less than 400 copies/mL (77% less than 50 copies/mL); the median CD4 count increase was 84 cells/mm<sup>3</sup>. Two patients experienced severe triglyceride elevations; one discontinued due to liver toxicity and another due to gastrointestinal symptoms. Phase III trials are planned for 2006.

Data from study TMC125-C223, a Phase IIb trial of Tibotec's new NNRTI, **TMC125** (now called **etravirine**), were presented at both EACS and ICAAC (*EACS abstracts LSPS3/7A and 7B; ICAAC abstract H-416c*). In the ICAAC report by Jeffrey Nadler, MD, 199 heavily treatment-experienced subjects with NNRTI- and PI-resistant HIV were randomly assigned to receive 400 or 800 mg TMC125 twice daily or an active control drug, plus an optimized background regimen. After 24 weeks, mean viral load reductions were 1.04, 1.18, and 0.19 logs, respectively; the corresponding percentages with viral load below 50 copies/mL were 21.3%, 17.7%, and 7.5%. The most common TMC125 side effects were diarrhea and skin rash; no common neuropsychiatric side effects (as seen with efavirenz) were reported. Severe (grade 3 or 4) side effects (about 40%) and laboratory abnormalities (about 30%) were common in the TMC125 and control arms alike. Tibotec is currently enrolling two Phase III studies of TMC125 plus TMC114 in treatment-experienced patients (see "Open Clinical Trials" on page 49). However, in December the company stopped a Phase II trial of TMC125 in PI-naïve subjects with prior NNRTI failure after preliminary data showed that the drug did not suppress HIV as well as approved PIs.

In the NRTI class, Paul Colucci presented data at ICAAC on **elvucitabine**, an experimental agent being developed by Achillion Pharmaceuticals (*abstract LB-27/Z*). With a half-life of more than 90 hours, the drug may potentially be administered just once weekly. In this study, 24 subjects received Kaletra plus either 5 or 10 mg elvucitabine once daily or 20 mg every 48 hours. After 21 days, viral load decreases were similar in the three arms: 1.8, 1.9, and 2.0 logs, respectively. Every-other-day dosing

suppressed HIV as effectively as daily dosing. A potential limitation is that the drug can cause bone marrow toxicity with decreased white blood cell counts at higher doses.

At the IAS meeting, Cal Cohen, MD, presented data on a new cytidine analog NRTI, **Reverset** (D-d4FC), being developed by Incyte (*abstract WeOaLB0103*). In a multi-center Phase IIb trial, 199 subjects resistant to other NRTIs were randomly assigned to receive one of three doses of Reverset or placebo as part of an optimized regimen. After two weeks, subjects in the 200 mg once-daily Reverset arm (the most effective dose) saw a 0.7 log reduction in HIV viral load, while HIV levels increased slightly in the placebo arm. Even subjects with 4–6 thymidine analog resistance mutations achieved a 0.6 log reduction. After four months, 54% of subjects experienced a greater than 90% decrease in HIV viral load, compared with 40% of those receiving placebo. Reverset was generally well tolerated and most side effects were mild. However, 12 subjects (34%) who took Reverset plus ddI developed severe (grade 4) pancreas enzyme elevations, and three who took Reverset plus ddI plus tenofovir developed frank pancreatitis. In addition, the data suggested that Reverset plus 3TC (lamivudine, Epivir)—also a cytidine analog—is not a potent pairing. On September 28, Incyte announced that the FDA did not approve its plan to begin a Phase III trial of Reverset by the end of 2005, instead requesting an additional Phase II study.

### PIPELINE AGENTS WORK IN NEW WAYS

While improvements in existing drug classes are welcome, agents that work by entirely novel mechanisms often generate the most excitement at medical conferences. At the EACS meeting, Javier Morales-Ramirez, MD, presented initial Phase II data on **MK-0518**, Merck's experimental integrase inhibitor (*abstract LBPS1/6*). After 10 days, 28 treatment-naïve subjects receiving various doses of MK-0518 twice daily experienced viral load decreases of 1.7–2.2 logs (about a 98% reduction), and about half achieved HIV viral loads below 400 copies/mL. There were no serious adverse events or discontinuations due to side effects. A longer 48-week dose-ranging trial is now underway.

Also at ICAAC, George Beatty, MD (a member of *BETA's* Scientific Advisory Committee) reported late-breaking data on Panacos' **PA-457**, the first HIV maturation inhibitor, which causes the virus to produce noninfectious progeny (*abstract H-416d*). In this 10-day Phase IIa study, 33 participants, about one-third of them treatment-experienced, were randomly assigned to receive one of four doses of PA-457 monotherapy or placebo. Subjects who received the highest tested dose (200 mg) achieved a median 1.03 log (90%) reduction in viral load. The agent appeared safe and well tolerated, with no observed dose-

limiting toxicities and no evidence of resistance. Because it targets a different stage of the HIV lifecycle, PA-457 should work against virus that is resistant to other drug classes, and due to its long half-life (60 hours), it may potentially be administered less than once daily. A Phase IIb trial is expected to begin this year.

Stanley Lewis, MD, of Tanox reported at ICAAC interim 24-week data on **TNX-355**, an investigational monoclonal antibody entry inhibitor (*LB-26*). In a Phase II study of 82 heavily treatment-experienced subjects with virological failure, those who added 10 mg TNX-355 to their optimized background regimens achieved better virological suppression than those who added placebo (mean viral load reduction of 1.19 vs 0.32 logs, respectively). No serious adverse events were attributed to the study drug and it did not cause CD4 cell depletion. Unlike CCR5 antagonists, TNX-355 works against HIV that uses either CCR5 or CXCR4 coreceptors (or both) to enter cells (*ICAAC abstract LB2-26*). Tanox plans to start a Phase III trial later this year.

Finally, further back in the pipeline, researchers from Sangamo BioSciences presented proof-of-concept data at ICAAC showing that human cells with genetically modified CCR5 coreceptors were protected from HIV infection in laboratory studies (*abstract H-1084*). The new gene therapy employs zinc finger nuclease enzymes designed to disrupt the CCR5 gene. When CCR5 expression was restored, cells were again susceptible to HIV entry. The company plans to file an Investigational New Drug application with the FDA in the second half of 2006.

### VALPROIC ACID: A POTENTIAL "CURE"?

Can a common epilepsy drug help eradicate latent viral reservoirs in the body—the key to the elusive “cure” for HIV? As Mario Stevenson, PhD, and Tae-Wook Chun, PhD, explained in a forum at the July IAS meeting (*debate TuDe04*), HIV (or its genetic material) remains dormant in long-lived immune cells, safe from antiretroviral therapy, which is active only against replicating virus. While HIV is thought to persist in latent (resting) cells, Chun and colleagues reported in the November 2005 *Journal of Clinical Investigation* that all 11 subjects analyzed in a recent study retained proviral HIV genetic material in both active and resting CD4 cells, even after as many as nine years of successful antiretroviral therapy with undetectable viral loads. Stevenson and Chun agreed that current anti-HIV therapies—which suppress but do not completely arrest HIV replication—are unable to eradicate the virus. However, new treatments could conceivably accomplish this goal, including immune-based therapies, agents that activate latent cells (such as interleukin-2), drugs that better penetrate resting cells, or agents that target different HIV replicative enzymes (such as integrase or RNase).

**Lipoatrophy and lipohypertrophy are two separate processes, rather than “redistribution” of fat from one site to another.**

The anticonvulsant drug valproic acid (also known as divalproex; brand names include Depakote and Depakene) may be such an agent, according to a proof-of-concept study described in the August 13, 2005 issue of *The Lancet*. Noting that an enzyme called histone deacetylase 1 (HDAC1) is necessary to maintain HIV in its dormant state within resting cells, David Margolis, MD, Ginger Lehrman and colleagues hypothesized that agents that inhibit HDAC1 might deplete latent virus; past laboratory studies have demonstrated that valproic acid can flush out HIV from resting CD4 cells. Four HIV positive subjects who had viral loads below 50 copies/mL for at least two years were given intensified antiretroviral therapy with T-20 for 4–6 weeks, then 500–750 mg valproic acid twice daily was added to their regimens for three months. The researchers found that the amount of replication-competent HIV hidden in resting CD4 cells declined by 68%–84% in three of the four subjects after the addition of valproic acid (the fourth experienced a smaller response), and that the treatment was well tolerated. While this study was small and brief, it suggests that new techniques for eradicating HIV are feasible. The authors concluded that intensified HAART plus an HDAC1 inhibitor safely accelerates HIV clearance from resting cells, stating, “This finding, though not definitive, suggests that new approaches will allow the cure of HIV in the future.”

Some experts sounded a less optimistic note, however, recalling that while previous attempts using similar methods appeared promising initially, patients did not remain virus-free over the long term. Robert Siliciano, MD, told the Associated Press that it was premature to talk about a potential cure for HIV, arguing that “even if you had one latently infected cell left, in a matter of days you would be back to where you started from.”

### HAART AND FAT ACCUMULATION

Everyone knows protease inhibitors cause abdominal fat accumulation, right? Not so, according to the latest results from the large Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study, reported in the October 1 issue of *JAIDS*. Peter Bacchetti, PhD, Carl Grunfeld, MD, and colleagues conducted a cross-sectional analysis of data from 425 HIV positive and 152 HIV negative gay and bisexual men aged 33–45, including MRI results, clinical assessments, and patient self-reports. They found that central lipohypertrophy (accumulation of visceral abdominal fat) was not associated with HIV infection or use of PIs; 40.2% of HIV positive men reported increased abdominal fat, compared with 55.9% of HIV negative control subjects. Peripheral lipoatrophy (fat loss in the face, limbs, and buttocks) was more common among HIV positive men, reported by 38.3% of this group versus just 4.6%

of HIV negative men. The researchers suggested that whatever weight gain occurred among men with HIV was likely due to aging and/or improved health (e.g., a lower rate of severe AIDS wasting syndrome in the HAART era), rather than HIV infection itself or antiretroviral therapy. Grunfeld acknowledged, though, that normal weight gain may appear excessive on a person with wasted limbs. Lipoatrophy was linked to use of d4T (stavudine, Zerit), as expected, but also to indinavir (Crixivan), which has more commonly been blamed for fat gain; nevirapine (Viramune) was associated with less central fat. Peripheral fat loss and central fat accumulation were not closely associated with each other—men who lost fat in their faces and limbs lost abdominal fat as well—adding to the evidence that lipoatrophy and lipohypertrophy are two separate processes, rather than “redistribution” of fat from one site to another.

### INSULIN RESISTANCE AND DIABETES

Another recent study suggests that PIs also might not be responsible—or solely responsible—for blood glucose abnormalities seen in people with HIV. As reported in the September 2, 2005 issue of *AIDS*, Todd Brown, MD, and colleagues analyzed prospective data from 533 HIV positive and 755 HIV negative gay and bisexual men in the Multicenter AIDS Cohort Study (MACS) collected at six-month intervals between 1999 and 2003. The researchers found that HIV positive men as a group were more likely to have higher fasting blood glucose levels, higher blood insulin levels, and greater insulin resistance compared with HIV negative men, regardless of what type of antiretroviral therapy they were taking; 36% of HIV positive men had insulin levels above 15 µU/mL vs 22% of HIV negative men. Even HIV positive men not taking any antiretroviral therapy had a higher rate of insulin resistance compared with HIV negative subjects. In addition, individuals with lower nadir (lowest ever) CD4 cell counts were also more likely to develop insulin resistance. Cumulative use of either PIs or NNRTIs was not associated with greater rates of insulin resistance. However, each additional year of NRTI use upped the odds of having an elevated insulin level and—as with lipoatrophy—d4T was the most common culprit; 3TC (but not AZT or ddI) was also associated with increased risk of insulin resistance.

The latest results from the large ongoing D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study reveal about a 6% rate of new-onset diabetes mellitus. As reported at the IAS meeting, Caroline Sabin and an international group of colleagues analyzed data from 22,749 HIV positive individuals on HAART who did not have diabetes at study entry. Within this cohort, 435 patients received a new diabetes diagnosis, for an incidence rate of 5.89 cases per 1,000 PY. Risk factors included older age,

male sex, black race, higher body weight, and smoking. In contrast to Brown's findings, in the D:A:D study use of PIs was associated with a slight—but significant—increase in the risk of diabetes; the researchers suggested that this link may be related to the effect of PIs on triglyceride levels.

On the other hand, a study by Clara Jones, MD, and colleagues from Tufts (published in the October 1, 2005 issue of *JAIDS*) found that among HIV positive individuals in the Nutrition for Healthy Living cohort, CD4 cell count, viral load, and number of years living with HIV were not associated with degree of insulin sensitivity. However, insulin resistance was associated with both PI-based and NNRTI-based HAART in HIV positive men. These results conflict with a Women's Interagency Study analysis (published in the May 1, 2005 issue of the same journal), which found that insulin sensitivity was not affected by either HIV or HAART. Further longer-term research is needed to determine why different studies find inconsistent links between blood glucose abnormalities, HIV infection, and antiretroviral therapy.

## LIPODYSTROPHY TREATMENT

Several recent conference presentations and journal articles have covered treatments for lipodystrophy and dyslipidemia (blood lipid abnormalities). Data from the RAVE study presented at ICAAC by Graeme Moyle, MD, showed that patients who switched from the thymidine analogs d4T or AZT to abacavir (Ziagen) or tenofovir experienced modest improvements in lipoatrophy—gaining limb fat—but tenofovir was associated with fewer side effects and greater reductions in triglyceride and LDL (“bad”) cholesterol levels (*abstract H-340*). In another study, treatment-naïve individuals who took the newer PI atazanavir (Reyataz) were less likely to experience elevated blood lipids than those taking nelfinavir (Viracept); as a consequence, researchers estimated that the atazanavir group had a significantly lower 10-year risk of developing cardiovascular disease (*abstract H-348*). Also, Eugenia Negredo, MD, and colleagues from Spain presented data from a study of 22 HIV positive individuals on HAART with elevated baseline LDL cholesterol and normal triglyceride levels who added ezetimibe (Zetia), an agent that inhibits cholesterol absorption in the gut, to their existing pravastatin (Pravachol). At 24 weeks, total cholesterol levels were down by 5%, LDL by 7%, and triglycerides by 8%; interestingly, lipid levels were lower at six weeks, then rebounded. No interactions between ezetimibe and Kaletra or nevirapine were observed (*abstract H-336*).

According to a study published in the July 1, 2005 issue of *AIDS*, lipid-lowering medications work better than switching antiretroviral drugs when it comes to dyslipidemia. In

this open-label study, Leonardo Calza, MD, and colleagues from Italy randomly assigned 132 HIV positive subjects with elevated blood lipids to either switch from their PIs to efavirenz or nevirapine—since NNRTIs are less associated with lipid abnormalities—or to stay on their PIs and add pravastatin or bezafibrate (a fenofibrate drug, in the same class as gemfibrozil [Lopid], that is not approved by the FDA). After 12 months, subjects who switched to NNRTIs experienced an average 19% decrease in total cholesterol, compared with an average 41% drop among those taking lipid-lowering medications; the corresponding decreases in triglyceride levels were 18% and 44%. At the Dublin lipodystrophy workshop, Patrick Mallon, MD, and colleagues from Australia reported that in a 33-person study, pravastatin—in addition to its lipid-lowering effect—improved lipoatrophy (average limb fat gain of 0.72 kg) more than discontinuing d4T or AZT (*abstract 23*). Based on another small study of 16 subjects, Calza's team found that the most recently approved statin drug, rosuvastatin (Crestor), was safe and effective in reducing lipids at 24 weeks, with a 31% decrease in total cholesterol and a 21% decrease in triglycerides; until larger studies are conducted, however, rosuvastatin should be used with caution since it can cause rhabdomyolysis, a serious form of muscle toxicity.

Jeroen van Wijk, MD, and colleagues from the Netherlands presented results from a trial comparing rosiglitazone (Avandia) versus metformin (Glucophage) at ICAAC (*abstract H-339*) and in the September 6, 2005 *Annals of Internal Medicine*. In this open-label study, 39 HIV positive men with lipodystrophy were randomly assigned to receive one of the two agents for six months. Rosiglitazone was associated with increases in body weight and both subcutaneous (under the skin) and visceral (internal) abdominal fat; fat loss did not improve, however, in patients taking d4T. Metformin, in contrast, was linked to decreases in body weight, total body fat, subcutaneous and visceral abdominal fat, and greater reductions in fasting lipid levels. Changes in insulin sensitivity were similar in both groups, but only rosiglitazone was associated with increased levels of adiponectin (a hormone produced by fat cells that helps regulate glucose metabolism). About one-third of patients taking metformin experienced gastrointestinal side effects, while rosiglitazone was well tolerated; liver toxicity was not seen in either group. The authors concluded that while rosiglitazone may partially correct fat loss, metformin improved visceral fat accumulation, fasting lipid profiles, and endothelial (blood vessel) function. Thus, they recommended that treatment should be individualized based on the specific nature of a patient's lipodystrophy-related symptoms.

## HAART REDUCES TRANSMISSION AMONG HETEROSEXUAL COUPLES

Combination antiretroviral therapy dramatically reduced the risk of HIV transmission among heterosexual couples in a Spanish study reported in the September 1, 2005 issue of *JAIDS*. Jesus Castilla, PhD, and colleagues studied 393 steady serodiscordant (mixed-status) heterosexual couples in which the uninfected partner reported no other risk factors. Before the advent of HAART, the HIV transmission rate was 10.3%, compared with 1.9% after the use of combination therapy was well established—a decline of about 80%. Looking at the data another way, the transmission rate was 8.6% among couples in which the HIV positive partner was not taking HAART, while none of the HIV negative individuals contracted the virus if their HIV positive partners were using effective combination therapy. In contrast to some past research, the presence of sexually transmitted infections in the HIV positive partner was not significantly associated with increased risk of HIV transmission. The reduction in transmission risk is likely attributable to low or undetectable viral load in individuals on effective treatment. The authors warned, however, that transmission remains possible and mixed-status couples should continue to practice safer sex even if the HIV positive partner is taking HAART.

## CRYSTAL METHAMPHETAMINE AND HIV

Increasing attention has focused lately on the use of crystal methamphetamine—especially among gay men—and its connection to HIV/AIDS. This past August, more than 900 public health officials, care providers, and patient advocates gathered in Salt Lake City for the first National Conference on Methamphetamine, HIV and Hepatitis, sponsored by the Salt Lake City Harm Reduction Project and the New York City-based Harm Reduction Coalition. In her keynote address, Patricia Case, PhD, from Harvard Medical School questioned whether methamphetamine use is, as many have asserted, a new “epidemic,” arguing that stimulant use has long been widespread in the United States. Conference attendees discussed the physiology of methamphetamine use, its sociological impact, its effects on sexual desire and behavior, harm reduction and addiction treatment, and the current state of research, as well as the need for more funding and better collaborative efforts to address crystal use and its impact on the transmission of HIV and viral hepatitis. Much remains to be learned about the impact of crystal on HIV transmission, disease progression, and treatment. For a comprehensive overview of the conference, see Bob Huff’s report in the July/August 2005 issue of *GMHC Treatment Issues*.

Gay and bisexual men who use crystal may triple their risk of HIV infection, according to a report in the September 2, 2005 issue of *AIDS*. Kate Buchacz, PhD, and colleagues examined the link between amphetamine use and HIV incidence among nearly 3,000 men who have sex with men (MSM) visiting AIDS Health Project anonymous test sites in San Francisco. They found that the HIV incidence rate was 6.3% per year among the 290 amphetamine users (10% of the total), compared with 2.1% per year among the 2,701 non-users. Among the 34 men who were infected with HIV in the previous six months, eight (24%) reported using amphetamine. The effect of crystal use was still apparent even after controlling for the use of alcohol and other recreational drugs. The increase is likely attributable, at least in part, to the fact that amphetamine users were more likely to engage in unprotected anal sex and more likely to report having 10 or more sexual partners in the past year.

Fortunately, education and prevention efforts in San Francisco may be having the intended effect. According to a survey by the Stop AIDS Project, methamphetamine use declined by 8% between the last six months of 2003 and the first six months of 2005; while 18% of 1,305 men surveyed during the first period said they used crystal in the past six months, this figure dropped to 10% among the 809 men surveyed during the second period. Willi McFarland, MD, of the San Francisco Department of Public Health (SFDPH) said this was the first time such a downward trend has been seen, and suggested it might help explain why the city’s rate of HIV infection among MSM has recently declined. H. Fisher Raymond of the SFDPH AIDS Office, however, said the decrease in crystal use is probably too recent to have contributed to the reduced HIV incidence rate.

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# Revisiting Monotherapy: *Heresy or Revised Orthodoxy?*

**Bob  
Huff**

**A**fter the widespread introduction of triple combination antiretroviral therapy in 1996 caused AIDS deaths to plummet, the earlier practice of single-drug treatment—or monotherapy—seemed like an embarrassing phase of medical ignorance. By then, it had become all too apparent that monotherapy promoted the rapid development of drug-resistant virus, often leading to treatment failure. Stories still occasionally surface about an isolated doctor prescribing solo AZT (zidovudine, Retrovir), and many long-time HIV physicians with large practices probably have one or two patients still doing well on two drugs and see no reason to change their regimens. But by and large, hitting hard with two nucleoside reverse transcriptase inhibitors (NRTIs) plus either a protease inhibitor (PI) or a non-NRTI (NNRTI) has become dogma, and is now enshrined in all HIV treatment guidelines.

## Straying from Dogma

That's why it seemed like heresy—or lunacy—when word came in 2003 that a doctor in Houston was conducting a study using only a single boosted drug, the PI combination pill Kaletra (lopinavir/ritonavir), in patients starting their first antiretroviral regimen. (Though Kaletra contains two PIs, it is still considered monotherapy when used alone since the small dose of ritonavir acts solely to enhance the effect of lopinavir.)

Joseph Gathe, MD, took his inspiration from an early Kaletra study showing that the ritonavir-boosted PI could hold its own against combination therapy by suppressing HIV viral load without NRTI support out to three weeks. Other reports had suggested that even when virological control was lost while using Kaletra, resistance mutations were rare. For Gathe, the risk/benefit assessment of treating without an NRTI safety net seemed to be swayed by the non-medical realities of his patients' lives. If dramatically simplifying the regimen meant that his patients could better afford their medicine, have fewer unplanned treatment interruptions, take more of their pills on time, stay adherent longer, and achieve better outcomes, then perhaps straying from dogma was not only justified, but was a wiser clinical judgment.

The problem of affordability was a central issue. With private insurance becoming harder to get and keep,

insurance copayments increasing, and government programs tightening access and starting waiting lists, the financial barriers to effective anti-HIV therapy were becoming an undeniable fact of life. So in 2002, with no support from government or industry, Gathe launched a pilot study with 30 patients attending a free clinic in an inner-city Houston neighborhood.

At the 43<sup>rd</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in September 2003, Gathe presented the 24-week results from his study. The aisle in front of his poster was extremely crowded. Much of the curiosity was generated by the fact that he dared to try such a radical strategy at all, while the characteristics of his study population also raised some ethical questions. The average viral load of his participants was over 200,000 copies/mL, and he allowed several individuals with viral loads in excess of 500,000 copies/mL to go on the single-drug plan. The majority also had CD4 cell counts well below 200 cells/mm<sup>3</sup>. Some felt it was irresponsible to include this vulnerable population in a pilot study.

Yet most who examined the data agreed that single-agent Kaletra had performed well, at least for those who managed to remain in the study. One worrying aspect to the data was the fact that only 22 of 30 patients were still participating at 24 weeks. But the stories of those who left the study served to illustrate the realities that thwart treatment

success for so many people with HIV/AIDS. One was deported, another had hepatitis B, and two quit the study due to toxicity. Unemployment and loss of insurance led to treatment failure for one participant who started stretching his medications by taking only one pill daily instead of three. Yet for those who stayed the course, the results were promising, with 95% of those on treatment having viral load suppressed below 400 copies/mL.

A year later, at the XV International AIDS Conference in Bangkok in July 2004, Gathe presented his final 48-week report. At the end of the study, 67% of the original 30 participants had a viral load below 400 copies/mL; no additional patients had disappeared after the initial 24 weeks. Overall, those who managed to stay in the study and stick to their regimens did fairly well. In the end, it was not an unqualified success, but the results focused attention on monotherapy and stimulated a handful of new pilot studies investigating variations on the concept, as well as some larger, more serious trials by Kaletra's manufacturer, Abbott Laboratories.

Gathe has consistently said that monotherapy should not be attempted outside of a clinical trial, and that larger studies for longer periods will be required before conclusions can be drawn about whether Kaletra monotherapy has a place in routine HIV care. But this hasn't stopped individual doctors and patients from attempting this strategy on their own, using solo Kaletra or other boosted PIs, on the basis of theory and the data from this limited study.

While Gathe studied patients who had never been on treatment, most subsequent studies of PI monotherapy have proceeded more carefully by excluding patients with extremely high viral loads or by investigating induction and maintenance as two separate stages, only switching patients to monotherapy after their HIV has been successfully suppressed using a conventional three-drug regimen. Unfortunately, the initial results from these studies have not been overwhelming.

## The OK Study

At the International AIDS Society (IAS) conference in Rio de Janeiro in July 2005, José Arribas, MD, reported results from the Abbott-sponsored Only Kaletra (OK) Study; the data were later published in the November 1, 2005 issue of the *Journal of Acquired Immune Deficiency Syndromes*. This was a randomized, open-label trial of continuing versus stopping NRTIs in 42 patients whose HIV was successfully suppressed on a Kaletra-based combination regimen. At 48 weeks, 95% of those who continued to receive triple combination therapy using Kaletra plus two NRTIs had viral loads below 50 copies/mL, compared with 81% of those taking Kaletra alone. Three patients (14%) in

the monotherapy group discontinued due to loss of viral suppression, and one other was lost to follow-up. The only discontinuation in the triple-drug group was due to elevated lipids (blood fats).

The good news is that the Kaletra-only patients who restarted their baseline NRTIs regained viral suppression with no evidence of resistance mutations. A comparison of residual viral load in responders in both arms using an extremely sensitive assay (accurate down to three copies/mL) showed no significant difference between the groups. This suggests that for certain patients, Kaletra monotherapy may work nearly as well as a triple-drug regimen. The challenge is predicting which individuals will benefit from treatment simplification.

Abbott had previously sponsored an 18-person trial looking at switching patients who had achieved viral suppression on a NNRTI-based triple-drug regimen (nevirapine [Viracept] or efavirenz [Sustiva] plus two NRTIs) to a simple maintenance regimen of Kaletra monotherapy. Participants were transitioned from their NNRTI to Kaletra over a two-week period, and then the two NRTIs were discontinued. When Gerald Pierone, MD, reported the 18-week results in 2004 at the Bangkok conference, 14 of 18 participants (78%) remained in the study, and 13 of those had viral loads less than 75 copies/mL. Three of the four who left the study dropped out due to diarrhea and the fourth discontinued when his viral load went above 1,000 copies/mL. In this small study, nearly a quarter of participants would have been better off staying on their original regimens. However, for nearly all of those who continued on treatment, simplification to Kaletra monotherapy led to continued viral suppression.

Kaletra causes gastrointestinal (GI) problems and blood lipid elevations that make it difficult for some patients to tolerate the medication for extended periods of time. [Editor's Note: a new formulation of Kaletra that reportedly produces fewer GI side effects was approved in October 2005; see "News Briefs" on page 3.] Pietro Vernazza, MD, and colleagues with the Swiss HIV Cohort decided to address this issue by switching 24 patients with fully suppressed virus to monotherapy maintenance using boosted atazanavir (Reyataz), a PI that does not raise blood lipids and may be more tolerable than Kaletra. At 24 weeks, 22 of 24 patients in this open-label study continued to have viral load below 50 copies/mL. The study also looked at HIV levels in cerebrospinal fluid and semen. Preliminary results indicated complete or near complete viral suppression in those compartments. However, atazanavir does not enjoy the same reputation for potency that Kaletra does; more evidence is needed to verify whether atazanavir is equally effective in suppressing the virus.

## Wave of the Future?

There is still more data to come. Abbott has completed—but not yet reported—a 138-person study of single-agent Kaletra versus a conventional Kaletra-based combination regimen. The company limited the entry criteria to people with viral loads less than 100,000 copies/mL and CD4 cell counts above 100 cells/mm<sup>3</sup> in this treatment-naïve study. Abbott is also sponsoring an ongoing 150-person trial comparing a triple-drug Kaletra-based regimen against a dual-drug combination consisting of Kaletra backed up by tenofovir DF (Viread). This trial, with its extra tenofovir safety net, will take all previously untreated patients with detectable viral load above 400 copies/mm<sup>3</sup> and any CD4 cell count (see “Open Clinical Trials” on page 48). Finally, Abbott is planning an induction/maintenance study of Kaletra simplification in people coinfecting with HIV and hepatitis C virus (HCV). Meanwhile, back in Houston, Gathe is continuing to investigate his concept with a 40-person open-label study in treatment-naïve patients that will run for 48 weeks.

### Another Type of Monotherapy

The use of monotherapy appeared in another study reported at the IAS conference in Rio, although this one did not attempt to maintain viral suppression with only one drug. It has been observed that HIV that has developed resistance to 3TC (lamivudine, Epivir) may be less able to replicate as efficiently as wild-type virus. Some researchers have proposed that continuing 3TC in a regimen even after resistance has emerged could perhaps keep the hobbled HIV in play, thus offering the benefits of a less harmful virus.

Antonella Castagna, MD, and colleagues took this concept one step further and compared the impact of continuing or stopping 3TC monotherapy on the rate of CD4 cell decline in people who had decided to undergo a treatment interruption. The participants all had prior documented 3TC resistance. By 48 weeks after discontinuing their complete regimens, fewer patients who continued to take 3TC alone had experienced a defined failure (an HIV-related symptom or a CD4 count below 350 cells/mm<sup>3</sup>) than those who stopped everything (44% vs 68%, respectively). The authors concluded that, “3TC monotherapy induces less immunological and clinical failure than treatment interruption.”

Even if monotherapy proves imperfect in these larger ongoing trials, a limited acceptance of the concept and wider use in practice may still be driven by the factors that initially motivated Gathe. Individuals using private insurance, Medicaid, or AIDS Drug Assistance Programs (ADAPs) might opt for simplification to reduce copayments by one-half to two-thirds—or may be pressured to do so by third-party payers eager to cut costs. But monotherapy not only reduces financial costs: simplified regimens could also offer reduced toxicity and increased adherence.

If the ongoing studies show that the risk of resistance is low and that viral load can be reliably rolled back by returning to a combination regimen, then many may be tempted to give monotherapy a try. Still, the evidence from the trials in progress will have to be strongly convincing to dislodge the accepted practice of combination therapy that has served so many so well. (One source of resistance could be the pharmaceutical industry, which has a strong incentive to see that the number of drugs required for treating HIV does not shrink from three to one.) If the risks are seen to be acceptable, and catastrophes few, it is possible that monotherapy—for the right patients, at the right time—may eventually find a niche as a viable and useful strategy for treating HIV disease.

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

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# Nutrition and HIV

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Highleyman

Good nutrition is key to a healthy lifestyle, regardless of whether one is living with HIV/AIDS. Optimal nutrition can help boost immune function, maximize the effectiveness of antiretroviral therapy, reduce the risk of chronic illnesses such as diabetes and cardiovascular disease, and contribute to a better overall quality of life.

In the early years of the AIDS epidemic, many people with HIV were dealing with wasting and opportunistic infections (OIs) linked to unsafe food or water. While these problems are less common today in developed countries with widespread access to highly active antiretroviral therapy (HAART), many HIV positive people have traded these concerns for worries about body shape changes, elevated blood lipids, and other metabolic complications associated with antiretroviral therapy.

Fortunately, maintaining a healthy diet can help address these problems. As HIV positive people live longer thanks to effective treatment, good nutrition can also help prevent problems (such as bone loss) associated with normal aging. But there is no single, optimal eating regimen appropriate for every person living with HIV/AIDS. Instead, HIV positive people should adopt a sensible balanced diet and consult an experienced nutrition specialist for individualized recommendations.

## Food for Life

Food is essential for life, providing the fuel the body needs to function and the building blocks that make up cells, tissues, and organs. The energy provided by food is expressed in terms of calories. The body requires a certain number of calories simply to carry out its basic metabolic functions such as respiration and maintenance of body temperature. Additional calories are needed to support physical activity, fight infection, and rebuild damaged tissues.

If a person does not take in enough calories, fat is broken down to provide fuel. Once the fat is consumed—or if an individual's metabolism is disrupted due to illness—lean

body mass (muscles and organs) is then used for fuel and raw materials. Conversely, if a person takes in more calories than needed, the extra energy will be stored as fat. The average person needs about 10–20 calories per pound (depending on physical activity level and other factors) to maintain a stable body weight; this requirement is likely to be higher for people with HIV, especially those with advanced disease.

But all food is not equal. While all contain calories, different foods vary widely in the nutrients they provide. A balanced diet is comprised of the following components.

**Protein:** Protein provides the building blocks of lean body mass. When a

protein-rich food is consumed, it is broken down into amino acids, which are reassembled to create enzymes, hormones, and bodily tissues. Most nutrition experts recommend that protein should contribute about 15–20% of the total calories in a person's diet. Good sources include meat, poultry, fish, eggs, dairy products, tofu, nuts, and legumes (e.g., dried beans, lentils).

**Carbohydrates:** Carbohydrates, which are converted to glucose in the body, are a primary source of energy. Carbohydrates are classified as simple or complex; complex carbohydrates take more time to break down, and thus provide fuel over a longer period of time. Despite the recent popularity of “low carb” diets, most nutrition

experts recommend that carbohydrates—primarily complex ones—should make up at least 50% of one's total daily calorie intake. Simple carbohydrates are found in processed sugar, honey, fruit and juice, and lactose (milk sugar). Complex carbohydrates are found in grain products such as bread, pasta, and rice; legumes; and starchy foods such as corn, potatoes, winter squash, and root vegetables.

**Fats:** Fat in food is a source of energy and has a high concentration of calories. Excess energy from any source—not just fatty food—is converted to fat in the body and stored for later use. Cholesterol (found in animal products like meat and eggs) and triglycerides are present in food, but are also produced when the body metabolizes sugar and saturated fat. Everyone needs some dietary fat, but getting too little is rarely a problem. More important is the type of fat. Saturated fats promote elevated blood levels of low-density lipoprotein (LDL) “bad” cholesterol, which can clog arteries and increase the risk of cardiovascular disease. Saturated fat is found in meat, butter, tropical oils (e.g., coconut, palm), and “trans” fats or hydrogenated oils (which are chemically altered to make them solid at room temperature). Polyunsaturated fats (found in safflower, sunflower, corn, and soybean oils) are generally considered more healthful, and mono-unsaturated fats (found in olive and canola oils, nuts, seeds, and avocados) can help raise levels of high-density lipoprotein (HDL) “good” cholesterol, which protects against heart disease. A balanced diet also contains essentially fatty acids, including omega-3 (found in flax and cold-water fish). Most experts say fats should make up no more than 25–30% of total calorie intake, with less than 10% being saturated fat.

**Fiber:** Also known as “roughage,” fiber is indigestible plant matter such as cellulose. Insoluble fiber plays an important role in digestion, helping

food move smoothly through the colon (large intestine); this type of fiber is found in the skin and pulp of many fruits and vegetables, whole grains, popcorn, and seeds. Soluble fiber helps stabilize blood sugar and may reduce LDL cholesterol levels; this type of fiber is found in oatmeal and oat bran, legumes, nuts, and fruits such as apples, oranges, pears, and grapes.

**Vitamins and minerals:** Along with the “macronutrients” described above, a balanced diet also contains many “micronutrients,” organic and inorganic substances necessary for proper biological functioning. Water-soluble vitamins (B and C) are excreted in the urine and must be consumed more often; fat-soluble vitamins (A, D, E, and K) are stored in the liver and can reach toxic levels if taken in large doses. Most vitamins must be obtained from food, although the body manufactures vitamin D when the skin is exposed to sunlight and others are produced by bacteria in the gut. Minerals (including the electrolytes chloride, potassium, and sodium) are inorganic substances found in the environment. The body needs several trace elements in tiny amounts, including boron, chromium, cobalt, copper, iodine, manganese, molybdenum, selenium, and zinc. Cooking and processing can destroy some vitamins and minerals. For information on the function and food sources of specific vitamins and minerals, see the chart on page 30.

**Antioxidants:** Free radicals are unstable oxygen molecules that contain unpaired electrons. This allows them to set off damaging chain reactions when they bind with and “steal” electrons from other molecules in the body—a process known as oxidative stress. Antioxidants scavenge and neutralize free radicals. By disrupting the oxidation process, antioxidants help protect cells from damage. Antioxidants include vitamins C and E, beta-carotene, the minerals selenium and zinc, and glutathione.

**Phytochemicals:** Among the advantages of obtaining nutrients from a balanced diet rather than supplements is that there are substances in whole foods that may offer unrecognized benefits. While most vitamins and minerals were isolated early in the 20th century, plant compound called phytochemicals are just now being discovered. Among these are allyl sulfides (found in garlic and onions), anthocyanins (in blueberries and blackberries), carotenoids (including beta-carotene in orange fruits and vegetables, lycopene in tomatoes, and lutein in dark green leafy vegetables), catechins (the tannins in green and black tea), flavonoids (in dark chocolate, red wine, tea, and many fruits), isothiocyanates (in broccoli and other cruciferous vegetables), limonoids (in citrus fruits), and sulforaphane (also in cruciferous vegetables). Some phytochemicals work as antioxidants, but others appear to have different mechanisms of action.

## How HIV Impacts Nutrition...and Vice Versa

In the early years of the epidemic, healthcare providers soon learned that people with AIDS commonly experienced both overt protein/calorie malnutrition and deficiencies of specific nutrients. But nutrient depletion may also begin to occur earlier in the course of HIV disease, even among individuals with relatively intact immune systems. Several factors can contribute to nutritional problems in people with HIV/AIDS.

**Malabsorption:** HIV or associated infections can damage the lining of the gastrointestinal tract, which can interfere with absorption of nutrients. Some HIV positive people experience specific problems, such as fat malabsorption, which can impair absorption of fat-soluble vitamins.

**Opportunistic infections:** Various bacterial, viral, fungal, and parasitic infections can interfere with proper

nutrition. Malignancies (cancers) and mycobacterial illnesses such as tuberculosis are often characterized by wasting. Several OIs cause vomiting and diarrhea, which can lead to poor absorption or loss of nutrients. Other infections—such as thrush (oral candidiasis), gingivitis (gum inflammation), and cytomegalovirus esophagitis (throat inflammation)—can make eating painful.

**Medications:** Antiretrovirals, OI drugs, and other medications can contribute to nutrient deficiencies and imbalances, either due to direct drug-nutrient interactions or drug side effects. Vomiting and diarrhea can lead to dehydration and depletion of nutrients. Loss of appetite (anorexia), fatigue, and taste alterations can make it difficult to eat enough. Antibiotics may interfere with nutrition by killing off beneficial bacteria in the gut. Food requirements—the need to take medications either on a full or an empty stomach or with specific types of food—can disrupt normal eating patterns. Finally, some antiretroviral medications are associated with metabolic changes such as blood lipid and glucose abnormalities.

**Inadequate intake:** Ill people often experience anorexia. OI symptoms and medication side effects—nausea, diarrhea, sore mouth or throat, altered sense of taste or smell—can further reduce the desire or ability to eat. This may be compounded by lack of money, depression, or feeling too fatigued to shop and prepare food.

**Altered nutritional requirements:** By altering metabolism (how the body processes and uses nutrients), acute or chronic illness—including HIV disease and OIs—and the resulting immune response can increase the body's energy needs. People with HIV/AIDS may require more calories, macronutrients, and specific vitamins and minerals. Chronic illness may also alter hormone and cytokine levels, which may have nutritional implications.

Conversely, nutritional deficiencies can impair immune function, potentially worsening HIV disease progression. Research has shown that depletion of vitamins A, C, and E, the B-complex vitamins, and the minerals selenium and zinc can interfere with cell-mediated immunity (CD4 cell, natural killer cell, and neutrophil proliferation and activation), antibody production, and normal cytokine signaling.

Studies looking at the prevalence of nutritional deficiencies in people with HIV/AIDS have produced conflicting data, but on the whole, depletion of nutrients (e.g., vitamins A and E, and minerals including magnesium, selenium, and zinc) appears to be common, especially among individuals with advanced disease. In particular, having HIV seems to decrease the body's store of antioxidants, as they are needed to offset increased oxidative stress. Researchers have uncovered evidence of subtle nutritional deficiencies among people who appear to be eating an adequate diet and are not suffering from frank protein/calorie malnutrition.

Experts don't yet understand the clinical significance—if any—of subtle changes in laboratory values relative to the norms seen in the HIV negative population, nor do they know how much of any given nutrient people with HIV/AIDS need for optimal immune function and overall health. Due to a lack of research on nutritional status in the setting of HIV disease, and because nutritional requirements vary dramatically from person to person, there are few definitive recommendations for nutritional supplementation in the HIV positive population.

## Waste Not, Want Not

Wasting—also known as cachexia—was a prominent feature of AIDS in the early years of the epidemic; even today, AIDS is referred to as “slim disease” in Africa. Experts define wasting as involuntary or unwanted loss of 10% or more of body

weight. As Steven Grinspoon, MD, and Kathleen Mulligan, MD, discuss in an April 2003 special issue of *Clinical Infectious Diseases (CID)* devoted to nutrition and HIV, “wasting...has been associated with increased mortality, accelerated disease progression, loss of muscle protein mass, and impairment of strength and functional status.” Even a 5% loss has been linked to increased illness and death.

In classic HIV-related wasting, lost weight is in the form of lean body mass rather than fat, especially in men. People with HIV/AIDS (and other chronic illnesses) require more calories simply to maintain their weight, due to increased metabolism, higher energy demands, hormone and cytokine imbalances, inefficient absorption and utilization of nutrients, and/or accelerated tissue breakdown (catabolism).

While effective antiretroviral therapy has dramatically reduced the incidence of severe wasting, moderate weight loss is still a prominent feature of HIV disease. For example, as reported in the September 1, 2005 *Journal of Acquired Immune Deficiency Syndromes (JAIDS)*, Alice Tang, MD, from Tufts University Medical School and colleagues found a steady increase in the rate of 5% or greater loss of body weight between 1995–1997 (pre-HAART) and 1998–2003 (HAART era). In an analysis of 713 HIV positive participants in the Nutrition for Healthy Living cohort, 53% lost at least 5% of their body weight during any six-month period. Weight loss was significantly associated with nausea, diarrhea, thrush, poverty, history of drug use, CD4 cell count below 200 cells/mm<sup>3</sup>, and HIV viral load above 100,000 copies/mL. The authors were unable to pinpoint the reasons for the increased rate of wasting in the HAART era.

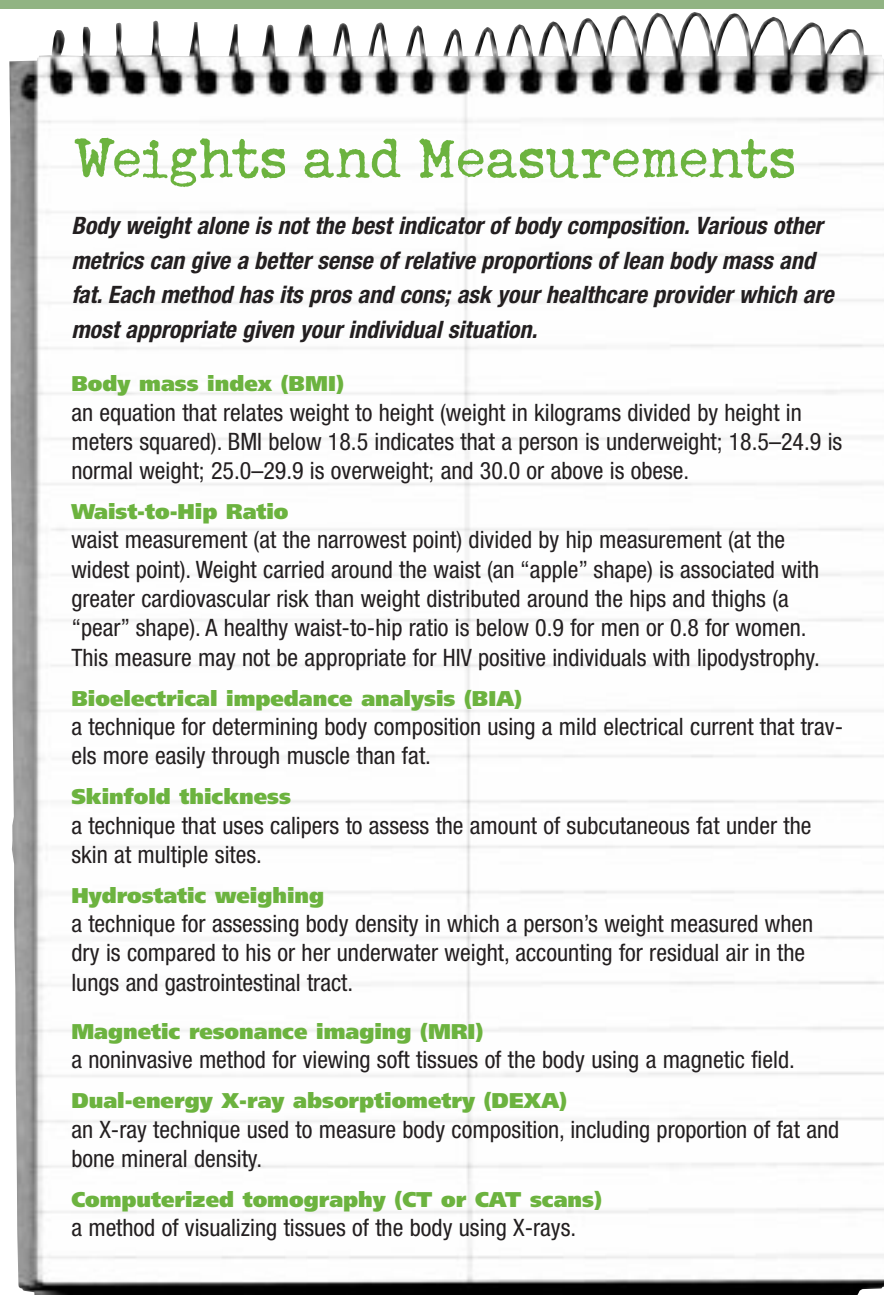
In another study (reported in the October 15, 2005 issue of *CID*), Adriana Campa, PhD, from Florida International University and colleagues found that 17.6% of 119 HIV

positive, mostly homeless drugs users in Miami showed evidence of HIV-related wasting. In this study, wasting was associated with cocaine and heavy alcohol use, “food insecurity” (not eating for one or more days in the past month), and higher HIV viral load. Participants taking HAART were more likely to experiencing wasting than those not receiving anti-HIV treatment (86% vs 67%).

Rather than dramatic whole-body weight loss, today many HIV positive people on HAART experience lipoatrophy, or fat loss in the face, limbs, and buttocks. Paradoxically, this may coincide with fat accumulation in other areas of the body (discussed below). Lipoatrophy is most strongly associated with use of nucleoside reverse transcriptase inhibitors (NRTIs), especially d4T (stavudine or Zerit). For this reason, U.S. government treatment guidelines no longer recommend d4T as part of a first-line regimen for people starting HAART.

Since HIV positive people and their clinicians may not recognize the early signs of wasting, it is important to monitor weight regularly to detect subtle changes. Underlying factors contributing to weight loss—such as OIs or hormone imbalances—should be promptly addressed. But, as Grinspoon and Mulligan point out, “no therapeutic guidelines currently exist for the management of weight loss and wasting in HIV-infected patients.”

When it comes to weight loss, prevention is often easier than cure. To add calories, focus on proteins and complex carbohydrates rather than “junk food” that contains mostly sugar and fat. Consider eating several small meals and snacks throughout the day rather than two or three large meals. Nutritional supplements such as Ensure or Boost may benefit individuals who find it difficult to eat solid foods. Some cities offer food delivery programs for people with HIV/AIDS who are unable to shop or prepare meals (e.g., Project Open Hand in San Francisco, God’s Love



## Weights and Measurements

*Body weight alone is not the best indicator of body composition. Various other metrics can give a better sense of relative proportions of lean body mass and fat. Each method has its pros and cons; ask your healthcare provider which are most appropriate given your individual situation.*

### **Body mass index (BMI)**

an equation that relates weight to height (weight in kilograms divided by height in meters squared). BMI below 18.5 indicates that a person is underweight; 18.5–24.9 is normal weight; 25.0–29.9 is overweight; and 30.0 or above is obese.

### **Waist-to-Hip Ratio**

waist measurement (at the narrowest point) divided by hip measurement (at the widest point). Weight carried around the waist (an “apple” shape) is associated with greater cardiovascular risk than weight distributed around the hips and thighs (a “pear” shape). A healthy waist-to-hip ratio is below 0.9 for men or 0.8 for women. This measure may not be appropriate for HIV positive individuals with lipodystrophy.

### **Bioelectrical impedance analysis (BIA)**

a technique for determining body composition using a mild electrical current that travels more easily through muscle than fat.

### **Skinfold thickness**

a technique that uses calipers to assess the amount of subcutaneous fat under the skin at multiple sites.

### **Hydrostatic weighing**

a technique for assessing body density in which a person’s weight measured when dry is compared to his or her underwater weight, accounting for residual air in the lungs and gastrointestinal tract.

### **Magnetic resonance imaging (MRI)**

a noninvasive method for viewing soft tissues of the body using a magnetic field.

### **Dual-energy X-ray absorptiometry (DEXA)**

an X-ray technique used to measure body composition, including proportion of fat and bone mineral density.

### **Computerized tomography (CT or CAT scans)**

a method of visualizing tissues of the body using X-rays.

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The appetite stimulant megestrol acetate (Megace) tends to promote fat rather than muscle gain and can cause side effects including edema (swelling). Certain antidepressants and other medications may also enhance appetite. Some patients swear by medical cannabis or dronabinol (Marinol), a pill that contains a synthetic version of marijuana’s active ingredient, THC.

While recombinant human growth hormone (HGH, Serostim) is

FDA-approved for the treatment of HIV-related wasting, it is extremely expensive and can cause side effects including carpal tunnel syndrome, joint pain, and insulin resistance. Anabolic (muscle-building) steroids such as testosterone and oxandrolone (Oxandrin) help some patients gain weight, but can also cause adverse effects. Hormone replacement therapy is most useful for individuals who have low levels; there is little evidence that “supraphysiological” doses (higher than the natural physiological

range) are beneficial, and they may be harmful (see “HIV and Hormones” in the Summer 2004 issue of *BETA*). Research has shown that anabolic steroids work better when combined with resistance exercise; in fact, some studies suggest resistance exercise works better than steroids, without the cost or side effects.

## Too Much of a Good Thing

For many HIV positive people in the developing world today, severe overall wasting due to protein/calorie malnutrition is not a major concern. In fact, some research suggests obesity may be a bigger problem. For example, Valerianna Amorosa, MD, and colleagues from the University of Philadelphia reported in the August 15, 2005 issue of *JAIDS* that in a cohort of nearly 1,700 HIV positive individuals, 31% of men and 30% of women were overweight, and 11% and 28%, respectively, were obese (in contrast, just 9% overall experienced wasting). Obesity was not associated with age, income, employment status, education, history of injection drug use, HIV treatment, or viral load, but in women it was more common among African-Americans. In Tang’s study discussed above, the proportion of patients categorized as overweight was greater in the HAART era than before the advent of effective antiretroviral therapy (35% vs 30%). And HIV positive people are hardly alone: the National Center for Health Statistics reports that two-thirds of all Americans are overweight and nearly one-third of adults are obese—double the proportion in 1980.

While “garden variety” obesity remains common, HIV positive people on HAART may also experience accumulation of fat in specific areas of the body including the belly, breasts, and back of the neck (“buffalo hump”). This abdominal or truncal lipohypertrophy is composed of deep visceral fat surrounding the internal organs. Both lipoatrophy (described above) and lipohypertrophy are features of

lipodystrophy syndrome; however, as discussed in an article by Denise Jacobson, PhD, and colleagues from Tufts in the June 15, 2005 issue of *CID*, experts now recognize that these are two distinct processes, not simply redistribution of fat from one area to another.

Lipodystrophy syndrome also includes elevated blood lipid levels and blood glucose abnormalities (see “Insulin Resistance and Diabetes” in the Winter 2004 issue of *BETA*). While most research indicates that lipodystrophy is associated with antiretroviral therapy—in particular protease inhibitors (PIs)—it is likely a multifactorial condition related to long-term HIV infection or immune reconstitution, since some people who develop the syndrome have never taken HAART. In a recent study by Peter Bacchetti, PhD, and colleagues, for example, abdominal fat accumulation was not linked to HAART, and was actually more common among HIV negative than HIV positive men (see “News Briefs,” on page 12.)

Obesity, and in particular visceral abdominal fat, has been linked to increased risk of cardiovascular disease in the general population. While it is still uncertain whether HIV positive people on HAART have higher rates of heart attacks and strokes (studies have yielded mixed data), it is likely that traditional cardiovascular risk factors—advancing age, male sex, cigarette smoking, high LDL cholesterol and triglyceride levels, insulin resistance, elevated blood pressure, and being overweight—are as important for HIV positive people as for anyone else (see “Cardiovascular Disease in People with HIV” in the Summer/Autumn 2002 issue of *BETA*).

While early nutritional guidelines for people with AIDS often emphasized packing on the calories—adding cream, cheese, peanut butter, gravy, and the like to foods—many HIV positive people today would be better served by adopting a balanced, low-fat diet.

Lifestyle changes, including diet modification, weight loss (if needed), exercise, and smoking cessation, are the first line of defense against cardiovascular disease. In order to lose weight, HIV positive people must follow the same rules as everyone else: burn more calories than one takes in. But reducing the amount of fat and cholesterol in the diet is not always enough to reverse fat accumulation or bring blood lipids within a healthy range, and exercise may not have much effect on visceral fat. When this is the case, lipid-lowering medications (including the statin and fibrate classes) are often used. Altering one’s antiretroviral regimen to include drugs less linked to high blood fat—such as substituting atazanavir (Reyataz) for another PI—is often effective. Researchers have tried treating lipodystrophy with human growth hormone and anabolic steroids, with mixed results. Although it is not yet clear what are the best interventions to address increased cardiovascular risk among HIV positive people on HAART, experts agree that a healthy diet certainly can’t hurt, and is likely to be part of the solution.

## Healthy Diet Basics

A healthy diet provides adequate nutrition without a lot of empty calories. “Balanced” means eating a variety of foods from all the important food groups, since no food alone provides all the nutrients the body needs. The traditional Food Guide Pyramid offers guidelines about how much to eat from each food group. (The traditional food pyramid was replaced in 2005 with a new pyramid, an online tool at [www.MyPyramid.com](http://www.MyPyramid.com). Because the new pyramid is more difficult to interpret, however, many nutrition experts continue to use the traditional version.) It recommends 6–11 servings per day of grain products such as bread, cereal, rice, and pasta; 3–5 servings of vegetables; 2–4 servings of fruit; 2–3 servings of dairy products such as milk, yogurt, and cheese; 2–3 servings

of high-protein foods such as meat, poultry, fish, eggs, and legumes; and small amounts of fat, oil, and sugar.

This may seem like a lot, but a “serving” is smaller than many people realize. A “serving” as per the guidelines would be, for example, a 3-ounce portion of cooked meat (about the size of a deck of playing cards), one chicken leg, a 2-inch cube of cheese, an 8-ounce glass of milk, a single tortilla or slice of bread, 5–6 crackers, one-third cup of cooked pasta, one-half cup of cooked vegetables, or one medium-size apple or orange. The amount of food typically served in restaurants, therefore, actually accounts for multiple “servings.”

The 2005 revision of the food pyramid focuses less on quantity and more on quality, while also emphasizing the importance of physical activity. At least half of one’s daily consumption of bread and cereal products should be comprised of whole grains; as a rule, less processed foods contain more nutrients. Simple carbohydrates tend to make blood glucose spike soon after eating and then fall, while complex carbohydrates tend to promote more stable levels over time. But what really matters is a food’s “glycemic index,” a measure of how quickly it is broken down in the body. Foods with a high glycemic index are broken down rapidly, causing blood sugar to rise sharply, while low glycemic index foods help the body maintain a steadier glucose level.

Eat vegetables of various colors—including dark green and deep orange—since these contain different vitamins, minerals, and phytochemicals. Whole fruit is preferable to juice, which is high in sugar and calories and typically lacks fiber. Since cooking can destroy vitamins, it is usually recommended to eat vegetables raw or lightly steamed. However, this may not be the best advice for people with severely compromised immunity who are at risk of infection with microorganisms that can be killed by cooking.

In the dairy group, select low-fat or non-fat products. People who choose not to consume dairy foods should be sure to obtain enough calcium from other sources. In the protein group, the new pyramid recommends eating more legumes, nuts, seeds, and fish—which contains heart-healthy omega-3 fatty acids. When eating meat or poultry, remove visible fat and skin. Broiling, baking, and grilling are healthier cooking methods than frying.

In terms of fats, avoid animal-derived fats and chemically altered hydrogenated oils, instead substituting plant-derived monounsaturated and polyunsaturated oils. This is good advice even for people who do not need to lose (or could stand to gain) weight, since animal fats increase the risk of cardiovascular disease. Fortunately, thanks to consumer demand, it is easier than ever to find commercial baked goods, snack foods, salad dressings, and the like that do not contain saturated fats. Another boon for the heart: a low-sodium diet can help keep blood pressure under control.

In addition to eating a balanced diet, it is also important to consume enough fluids. Experts traditionally recommend eight 8-ounce glasses of water per day. Herbal tea, broth, and fruit or vegetable juices can also be good fluid sources. But beverages that contain caffeine or alcohol have a diuretic effect, and can cause loss of water due to increased urination. It is especially important to drink enough fluid to prevent dehydration when suffering prolonged vomiting or diarrhea.

People with very low CD4 cell counts concerned about infections such as cryptosporidiosis due to contaminated tap water should use filtered or bottled water.

## Facts Versus Fads

The traditional dietary guidelines are not free of controversy. Some critics contend that in putting together the recommendations, the federal government has been unduly influenced by the food industry. They argue, for example, that adults really do not need to consume cow’s milk at all. Some believe the pyramid recommends more protein than most people need, while others argue that humans evolved to eat a “hunter-gatherer” diet much lower in carbohydrates.

“Low carb” diets (related to the Atkins plan) containing small amounts of carbohydrates and larger amounts of protein and fat have gained considerable popularity in recent years—so much so that many people have come to believe that carbohydrates *per se* are “fattening.” While such diets may produce temporary weight loss, they are usually short on fiber, can stress the liver and kidneys, and may lead to dangerously elevated blood lipid levels.

More people are also adopting vegetarian or vegan diets, which have been linked to reduced risk of cardiovascular disease and cancer. Most people can obtain adequate nutrition from a diet that contains little or no meat or other animal products, though this may be more challenging for growing children or people with chronic illness who have increased

Learn how to read the “Nutrition Facts” label, which contains a wealth of information about the nutritional content of packaged foods:

[www.cfsan.fda.gov/~dms/foodlab.html](http://www.cfsan.fda.gov/~dms/foodlab.html)

**“[A]ddressing obesity is likely to become an increasingly common part of the management of HIV infection.”**  
— David Wohl, MD

energy needs. The trick is to learn how to combine proteins from different sources (such as grains, legumes, nuts, and soy) to obtain a full complement of essential amino acids; vitamin B12 supplementation may also be needed.

An increasing number of health-care providers now recommend a “Mediterranean diet”—including olive oil, tomatoes, garlic, and red wine—since people from areas that consume such a diet tend to have lower rates of heart disease. A Japanese-style diet that contains lots of fish and soy products is also a healthy option.

Notwithstanding these caveats, the consensus recommendation to eat a range of foods from a variety of categories remains sound. Most experts suggest a breakdown of about 50–60% carbohydrates, 15–20% protein, and no more than 25–30% fat. But because individual nutritional needs vary widely, it is difficult to recommend a specific diet suitable for all people with HIV/AIDS. A trained dietitian who has experience working with HIV positive people can help devise an appropriate individualized eating plan.

## What About Supplements?

As a rule, it’s usually best to obtain nutrients from food. Swallowing handfuls of pills will not make up for a poor diet. But even HIV positive people who eat well can have low levels of various important nutrients—at a time when their nutritional needs may be increased—and thus may benefit from supplementation. The U.S. government’s Daily Values (formerly known as Recommended Dietary Allowances) for nutrients do not

necessarily reflect the amount required for optimal health, just the minimum needed to stave off deficiency symptoms in the average healthy person. It is not yet known whether accepted recommended nutrient levels for the general population are adequate for people with HIV/AIDS.

Dietary supplements are products such as vitamins, minerals, amino acids, herbs, and antioxidants; they are usually taken orally in the form of tablets, capsules, powders, or liquids. Due to the lack of strict quality control and labeling requirements, marketed products can vary widely in contents, strength, and purity. Although regulated by the U.S. Food and Drug Administration (FDA), supplements do not need to undergo rigorous clinical trials of safety and efficacy as required for approval of pharmaceutical drugs. In fact—because there is little financial incentive to spend money developing products that cannot be patented—there have been few rigorous, controlled studies on the use of nutritional supplements in people with HIV.

In the mid-1980s, Barbara Abrams, DrPH, and colleagues from the University of California at Berkeley began a large observational study of dietary intake in 296 HIV positive men; results were reported in the August 1993 issue of *JAIDS*. By one measure, the risk of developing AIDS decreased as consumption of 11 different micronutrients increased—significantly so for riboflavin, vitamin E, and iron, and approaching significance for thiamin, niacin, and vitamin C. This study was susceptible to selection bias, however, since people

who ate healthier diets or took supplements might have had healthier lifestyles overall.

More recently, researchers in Thailand showed that a low-cost multivitamin and mineral supplement improved the survival of HIV positive people who were not taking HAART. As reported in the November 21, 2003 issue of *AIDS*, Sukhum Jiamton, MD, and colleagues conducted a double-blind, placebo-controlled trial in which nearly 500 HIV positive individuals with CD4 cell counts of 50–550 cells/mm<sup>3</sup> were randomly assigned to receive either a placebo or a supplement containing 12 vitamins, eight minerals, and the amino acid cysteine twice daily. After 48 weeks, about twice as many people died in the placebo arm compared with the supplement arm (15 vs 8 deaths); among those with baseline CD4 counts below 200 cells/mm<sup>3</sup>, the mortality rate was significantly lower in the supplement arm. On the other hand, an earlier study in Zambia found that multivitamin supplementation had no effect on CD4 cell count or mortality.

In the July 1, 2004 *New England Journal of Medicine*, Wafaie Fawzi, DrPH, from Harvard School of Public Health and colleagues reported on a double-blind, placebo-controlled study in which 1,078 HIV positive pregnant women in Tanzania received either daily supplements of vitamin A; a multivitamin supplement containing vitamins B, C, and E; or both. After a median follow-up of 71 months, 67 out of 271 women (24.7%) who received the multivitamin either died or progressed to advanced HIV disease (stage IV as defined by the World Health Organization), compared with 83 out of 267 women (31.1%) who received the placebo. Women in the multivitamin arm—but not those receiving vitamin A alone—also had significantly lower HIV viral load, higher CD4 and CD8 cell counts, and improved birth outcomes.

In a June 10, 2005 *AIDS* editorial reviewing the current state of knowledge about micronutrient supplement-

tation in people with HIV/AIDS, Tang and colleagues concluded that “a combination of vitamins may afford some benefits to undernourished HIV-infected populations, particularly those with more advanced disease,” but conceded that “the role of individual micronutrients...is less clear.” Most healthcare providers agree that HIV positive people can benefit from a daily multivitamin and mineral supplement. (Due to the potential harmful effects of iron, many recommend an iron-free supplement for anyone other than menstruating women and people with iron deficiency). But when it comes to specific nutrients, expert opinion—and the little relevant research conducted to date—remains sharply divided.

Higher amounts of various substances have been proposed to improve immune response, ameliorate symptoms and drug side effects, and slow HIV disease progression, on the basis of theoretical understandings about how an agent is expected to behave, laboratory research looking at the effects of a substance *in vitro*, cross-sectional studies showing specific nutritional deficiencies in a population, or—less commonly—controlled trials. Several nutrients that have received the most attention with regard to HIV/AIDS are discussed below.

### Vitamin A

Richard Semba, MD, from Johns Hopkins and colleagues reported in 1993 that among a cohort of 179 HIV positive and HIV negative injection drug users in Baltimore, vitamin A deficiency was linked to lower CD4 cell counts and increased risk of mortality. Two years later, he reported that vitamin A deficiency among pregnant HIV positive women in Malawi was associated with increased risk of mother-to-child HIV transmission (32% among deficient women vs 7% among women with normal levels) and higher infant mortality. Similarly, a U.S. study found that vitamin A-deficient women were about five times more likely to transmit HIV to

their babies. Some studies have found vitamin A deficiency to be associated with greater vaginal shedding of HIV and higher levels of virus in breast milk—although Fawzi’s study described above actually found a significantly *higher* rate of mother-to-child transmission via breast-feeding in women given vitamin A supplements.

Several large controlled studies looking at supplementation with vitamin A or beta-carotene (a vitamin A precursor) for HIV positive pregnant women in parts of Africa where frank deficiency is common, however, have failed to detect decreased rates of mother-to-child transmission; results have been mixed concerning reductions in miscarriages, premature births, and infant morbidity and mortality. In Fawzi’s Tanzanian study, vitamin A alone did not produce outcomes significantly different from those seen in the placebo arm, and adding vitamin A to the multivitamin seemed to reduce its beneficial effects. Since the benefits are unclear and high doses can cause liver toxicity and other problems, most experts do not recommend vitamin A supplementation—beyond the amount found in a typical multivitamin pill—for people with HIV/AIDS.

### Vitamin C

In laboratory studies, vitamin C has been shown to inhibit viral replication *in vitro*; it also plays an important role in tissue repair. Thus, it is not surprising that megadoses of this vitamin have been touted as a cure for everything from the common cold to cancer to HIV/AIDS. Controlled clinical trials comparing vitamin C to placebo for the treatment of colds and flus have yielded mixed results, and the data have been even less promising concerning HIV disease. While vitamin C deficiency does appear to impair various aspects of the immune response, research has not provided evidence that supplementation delays HIV disease progression or improves survival.

### Vitamin E

Vitamin E plays a role in metabolism and proper immune function, and laboratory studies suggest it has an antiviral effect. For example, Alonso Heredia, PhD, from the University of Maryland and colleagues reported in the May 20, 2005 issue of *AIDS* that addition of vitamin E to cell cultures from 10 HIV positive individuals significantly reduced HIV production, as indicated by p24 antigen levels. The authors suggested that supplementation might slow HIV replication enough to inhibit the emergence of drug-resistant virus in resting cells and to delay viral rebound after treatment interruption. But while low (or decreasing) levels of vitamin E have been linked to CD4 cell declines and HIV disease progression, this does not imply causality.

The jury is still out on the benefits and risks of high-dose vitamin E supplementation, but data from recent large studies in the HIV negative population do not look good. In the Women’s Health Study (a primary prevention trial that included nearly 40,000 healthy, HIV negative women), subjects randomly assigned to receive 600 IU of vitamin E every other day not only did not have reduced rates of cancer or cardiovascular disease relative to women in the placebo arm, but actually showed a nonsignificant *increase* in total mortality. Results of a meta-analysis of 19 clinical trials with a total of nearly 136,000 subjects published in the January 4, 2004 *Annals of Internal Medicine* led authors Edgar Miller, MD, and colleagues to conclude that, “High-dosage [400 IU or more daily] vitamin E supplements may increase all-cause mortality and should be avoided.” In the absence of large controlled studies in the HIV positive population, the same advice is sound for people with HIV/AIDS as well.

### Selenium

The trace element selenium—also known to play a role in proper

immune function—has received considerable attention as a treatment for HIV/AIDS and a variety of other diseases. Some *in vitro* research indicates that HIV requires selenium in order to replicate. A study of 125 HIV positive injection drug users by Marianna Baum, PhD, and colleagues from the University of Miami (published in 1997) revealed that after adjusting for various factors including CD4 cell count, selenium deficiency was significantly associated with increased mortality. “When all nutrient factors that are associated with survival are considered together,” Baum concluded in a later review article, “only selenium deficiency is a significant predictor of mortality.” And in a study of 670 HIV positive pregnant women in Tanzania (reported in the June 1, 2005 issue of *JAIDS*), Roland Kupka, DSc, from Harvard School of Public Health and colleagues found that low plasma selenium levels were associated with increased risk of miscarriage, infant death, and mother-to-child HIV transmission.

But the fact that low selenium levels are linked to worse disease progression does not necessarily mean supplementation will improve matters. HIV nutrition expert Mary Romeyn, MD, has reported anecdotal evidence that selenium supplementation leads to clearance of thrush. On the other hand, while low selenium levels were linked to increased likelihood of cervical dysplasia (precancerous cell changes) among HIV positive women in one study, selenium supplements did not reduce the risk.

And, as reported in the December 15, 2004 issue of *JAIDS*, Scott McClelland, MD, from the University of Washington and colleagues found that in a study of 400 nonpregnant HIV positive women in Kenya, supplementation with a multivitamin plus selenium led to increased vaginal shedding of HIV, which has implications for sexual and perinatal transmission. Among women who started out with normal selenium levels,

those who received supplements were more than twice as likely to shed HIV in their vaginal secretions and had higher vaginal HIV viral loads than women who received a placebo; a similar effect was not seen, however, in selenium-deficient women brought up to normal levels. While supplementation resulted in higher CD4 and CD8 cell counts, the authors concluded that, “The potential benefit of micronutrient supplementation in HIV-1-seropositive women should be considered in relation to the potential for increased infectivity.”

### Zinc

Zinc deficiency has been linked to impaired immune function and supplementation has been suggested as a treatment for people with HIV/AIDS, but studies to date have produced conflicting results. While some suggest that zinc enhances the body’s ability to fight HIV and improves disease symptoms, others have found it has a detrimental effect. In one study of injection drug users, lower zinc levels were associated with reduced CD4 cell counts, but this does not necessarily mean one caused the other. In an early nutritional survey of nearly 300 HIV positive men followed for seven years, high doses of zinc were associated with *faster* HIV disease progression. Some researchers have hypothesized that this may be related to the fact that HIV requires zinc-containing structures called “zinc fingers” to produce functional viral progeny.

More recently, Raziya Bobat, MD, and colleagues reported in the November 26, 2005 issue of *The Lancet* that in a randomized, placebo-controlled trial of 96 HIV positive South African children aged six months to five years, zinc supplementation for six months reduced the incidence of diarrhea and pneumonia, and did not appear to promote viral replication. Given the degree of uncertainty, most experts do not recommend zinc supplementation beyond the amount contained in a multivitamin and mineral pill.

### Antioxidants

Vitamin C, vitamin E, selenium, and zinc act as antioxidants, helping prevent cell damage caused by highly reactive free radicals (oxidative stress). While free radicals play a role in immune defense against invading pathogens, they can also harm surrounding cells. Research has shown that people with HIV and other chronic infections have higher levels of free radicals, which promote viral replication. Conversely, antioxidants appear to reduce oxidative stress, inhibit HIV activity, and possibly slow HIV disease progression. Antioxidants may also reduce liver fibrosis in people with hepatitis B or C and protect the liver from toxicity as it metabolizes drugs.

The body manufactures certain antioxidants as needed, but this process requires adequate amounts of several nutrients. Studies suggest that a major intracellular antioxidant, glutathione, may help reduce the rate of HIV disease progression. Nutrients that help raise glutathione levels include selenium, alpha-lipoic acid, N-acetyl-cysteine (NAC), acetyl-L-carnitine, L-glutamine, and coenzyme Q10. In one small study, high-dose NAC supplementation led to decreased HIV viral load. There have been several case reports and small studies in which supplementation with antioxidants or precursors including NAC, acetyl-L-carnitine, and coenzyme Q10 seemed to counter lactic acidosis (a sign of mitochondrial toxicity) related to antiretroviral therapy. What’s more, Andrew Hart, MD, and colleagues from the Royal Free and University College Medical School reported in the July 23, 2004 issue of *AIDS* that acetyl-L-carnitine supplements helped reverse nerve damage and alleviated the pain of peripheral neuropathy associated with certain NRTI drugs.

But antioxidant supplements may also have deleterious effects. In a small pilot study by Grace McComsey, MD, and colleagues from Case Western Reserve University (reported in the August 15, 2003 issue of *JAIDS*), while

## Good Nutrition is Not a Cure for HIV

While supplementing a range of micronutrients may contribute to improved health, this is not to suggest that nutritional supplements alone can take the place of HAART. A few years ago, South African Health Minister Manto Tshabalala-Msimang raised a furor when she suggested that people with HIV/AIDS should consume garlic, lemon, and olive oil, while her government was resisting efforts to expand access to antiretroviral therapy. This past May, UNAIDS director Peter Piot, MD, blasted vitamin entrepreneur Matthias Rath, who placed ads in South African newspapers promoting vitamins as a treatment for AIDS, claiming that antiretroviral drugs are toxic and cause birth defects. "Vitamins are no cure or treatment for AIDS," stated Piot, "and anybody who claims the contrary is a charlatan."

Nevertheless, according to World Health Organization Director-General Jong-Wook Lee, greater attention must be paid to the nutritional needs of people with HIV/AIDS in the developing world. "We do know that sound nutrition helps maintain the immune system, increases body weight, and boosts energy levels," he said at an April conference in Durban. "Most of the 30 million HIV-infected people in Africa don't even have secure access to the basic nutrients any human being needs to live a healthy life."

supplementation with vitamin C, vitamin E, and NAC slightly reduced elevated LDL cholesterol levels and abdominal fat accumulation in 10 subjects with HIV-related lipodystrophy, the antioxidants also raised blood glucose levels and worsened insulin resistance. "We should never assume that high doses of vitamins are safe," the authors cautioned. "They are not safe until clinical studies prove them to be safe."

### Omega-3 Fatty Acids

Omega-3 fatty acids, found in cold-water fish such as salmon and

herring, have been associated with reduced cardiovascular disease risk in the general population; one study of more than 4,700 adults over age 65 showed that eating fish 3–4 times per week was associated with a 30% reduction in congestive heart failure. In the November 15 issue of *CID*, David Wohl, MD, from the University of North Carolina at Chapel Hill and colleagues reported that omega-3 may also help address one cardiovascular risk factor in people with HIV/AIDS. In this open-label study, 52 HIV positive individuals on HAART with fasting

triglyceride levels above 200 mg/dL were randomly assigned to receive either omega-3 fish oil supplements (eicosapentaenoic acid and docosahexaenoic acid) plus nutritional counseling or else nutritional counseling alone. After 16 weeks, subjects receiving fish oil supplements experienced a 19.5% reduction in fasting triglyceride levels, compared with a 5.7% decrease in the counseling-only arm (though seemingly substantial, this difference was not statistically significant). However, LDL cholesterol levels increased by 22.4% in the fish oil arm, while remaining stable in the counseling-only arm; HDL levels did not change in either group. The authors acknowledged that "whether this increase [in LDL] attenuates any benefit in lowering triglyceride levels is unclear."

### Special Supplements

Various functional supplements have been developed to augment levels of particular compounds thought to have specific beneficial effects. For example, two small studies presented at the 7<sup>th</sup> International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV in November 2005 showed that a supplement called NucleomaxX—a sugar cane extract containing the nucleoside uridine—helped reverse lipoatrophy in individuals taking NRTIs. Jussi Sutinen, MD, and colleagues from Finland reported that in a study of 20 patients taking d4T or AZT (zidovudine, Retrovir), those taking NucleomaxX three times daily for 10 days gained significantly more arm and leg fat (about 900 grams) than subjects taking placebo; the NucleomaxX group also gained visceral abdominal fat. Likewise, McComsey reported that both patients and their physicians reported significant improvement in lipoatrophy in a study of 14 subjects taking d4T who received NucleomaxX three times daily every other day for 16 weeks. (An open-label Phase II study of NucleomaxX for lipoatrophy is currently enrolling; see "Open Clinical Trials," on page 51).

## More is Not Always Better

With all this conflicting data, it can be difficult for HIV positive people to make informed decisions about supplements. The bottom line, according to Judith Nerad, Mary Romeyn, and colleagues in the April 2003 *CID* special issue: “[T]here is little documentation in the literature that supplementation beyond what is recommended has had any impact on clinical outcome.” But, “[i]f a patient’s vitamin or mineral status is deficient, supplementation is clearly necessary.”

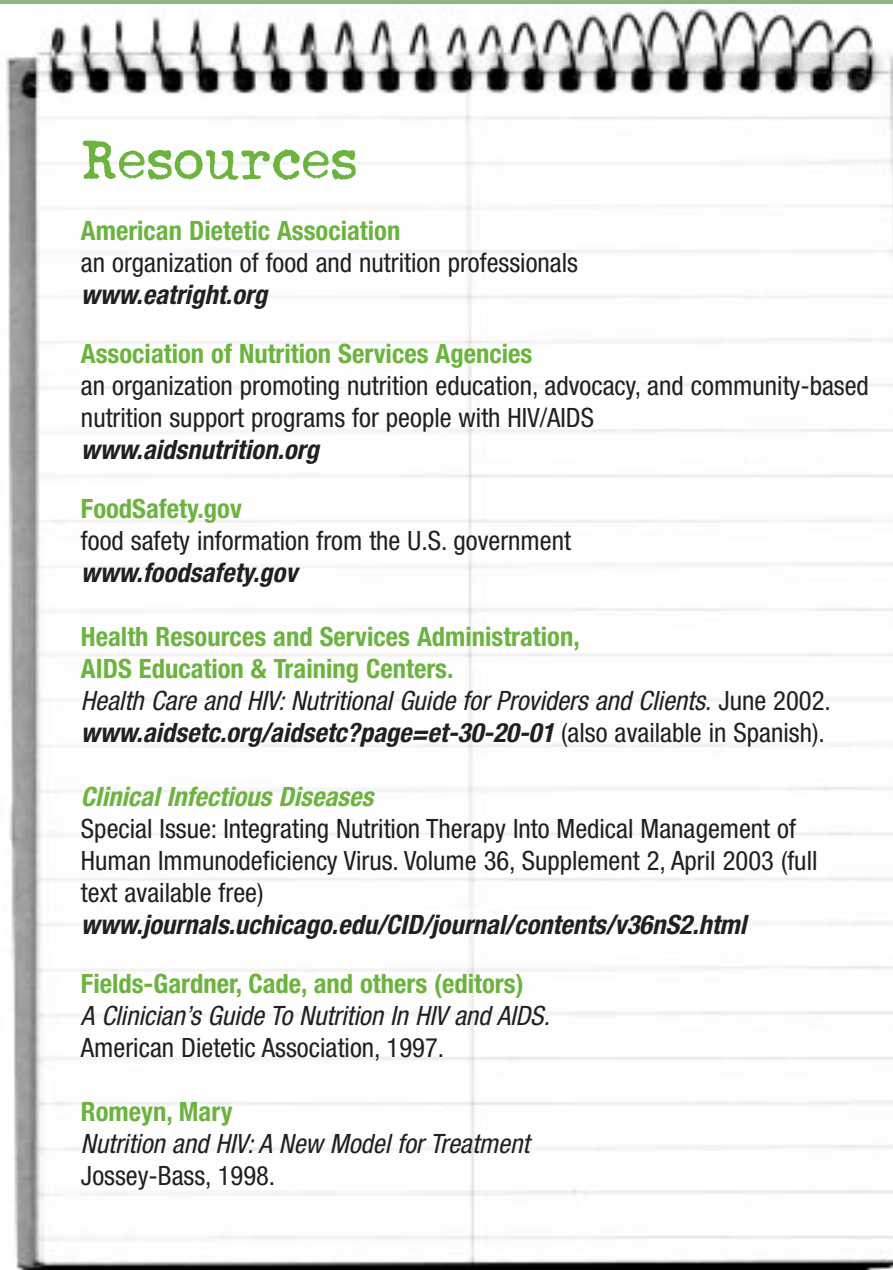
People with HIV/AIDS commonly have subtle nutritional deficiencies, and research to date has shown that daily multivitamin use is safe and at least potentially beneficial in this population. Different experts have suggested various supplementation regimens. For example, Romeyn—in her book *Nutrition and HIV: A New Model for Treatment*—suggests a basic regimen that includes:

- a multivitamin, without extra iron, twice daily;
- a trace element supplement once daily;
- an antioxidant supplement once daily.

Others, such as nutritionist Margaret Davis, RD, recommend only the multivitamin, plus increased consumption of fruits and vegetables.

As previously noted, nutritional needs vary widely from person to person, and there is no one diet or supplement regimen appropriate for all people with HIV/AIDS. Further, the presence of a nutrient deficiency does not necessarily mean supplementation is the solution, since poor absorption, underlying infections, metabolic changes, or hormone imbalances could be contributing to the problem.

When using supplements, do not take more than the recommended dose on the label unless advised to do so by a knowledgeable healthcare provider. As some of the studies



## Resources

### American Dietetic Association

an organization of food and nutrition professionals  
[www.eatright.org](http://www.eatright.org)

### Association of Nutrition Services Agencies

an organization promoting nutrition education, advocacy, and community-based nutrition support programs for people with HIV/AIDS  
[www.aidsnutrition.org](http://www.aidsnutrition.org)

### FoodSafety.gov

food safety information from the U.S. government  
[www.foodsafety.gov](http://www.foodsafety.gov)

### Health Resources and Services Administration, AIDS Education & Training Centers.

*Health Care and HIV: Nutritional Guide for Providers and Clients*. June 2002.  
[www.aidsetc.org/aidsetc?page=et-30-20-01](http://www.aidsetc.org/aidsetc?page=et-30-20-01) (also available in Spanish).

### Clinical Infectious Diseases

Special Issue: Integrating Nutrition Therapy Into Medical Management of Human Immunodeficiency Virus. Volume 36, Supplement 2, April 2003 (full text available free)  
[www.journals.uchicago.edu/CID/journal/contents/v36nS2.html](http://www.journals.uchicago.edu/CID/journal/contents/v36nS2.html)

### Fields-Gardner, Cade, and others (editors)

*A Clinician's Guide To Nutrition In HIV and AIDS*.  
American Dietetic Association, 1997.

### Romeyn, Mary

*Nutrition and HIV: A New Model for Treatment*  
Jossey-Bass, 1998.

discussed above illustrate, more is not necessarily better. A recent case underscores this warning. As reported in the September 2005 *International Journal of STD and AIDS*, an HIV positive man in London developed severe liver inflammation with skyrocketing ALT levels after taking more than a dozen dietary supplements, many at high doses—as much as 67 times the recommended daily value; fortunately, once he stopped taking the supplements, his liver function returned to normal.

Certain vitamins and minerals (including the fat-soluble vitamins A, D, and E) can be toxic at high doses, and they may cause deleterious effects even at lower doses beyond what is provided in a typical multivitamin pill. Remember that “natural” does not necessarily mean “safe.” Beware of any supplement touted as a “cure” for a range of ailments—if something sounds too good to be true, it probably is. Verify that health claims are supported by reliable research. Some supplements may not be harmful, but

simply a waste of money. Seek medical advice before starting a new supplement or beginning any unusual diet. Tell healthcare providers about any use of supplements (as well as over-the-counter medications, recreational drugs, and herbal remedies), since these can potentially interact with antiretroviral drugs.

## Eat Right for Life

Nutritional management should be a regular part of HIV/AIDS care. Even if an HIV positive person has no obvious nutritional problems such as wasting, a healthy diet can still help stave off illness and improve quality of life. But, as Tang and colleagues noted in their review, dealing with nutritional issues “may not be part of the traditional care or thought process of the HIV care provider.” A registered dietitian (RD) who has experience working with people with HIV/AIDS can be an invaluable resource.

The American Dietetic Association recommends a baseline nutritional and body composition assessment soon after HIV diagnosis. Follow-up assessments should be conducted at least once annually for asymptomatic individuals with well-controlled HIV disease, and every few months for patients with AIDS or known nutritional problems. Tasmin Knox, MD, from Tufts recommends anthropometric measurements of body composition (see the sidebar on page 21 for an explanation of various methods); laboratory tests of protein and micronutrient levels in the blood; tests of metabolic parameters such as blood lipids, blood glucose, and liver enzymes; and clinical assessment of eating patterns, supplement use, functional status, physical symptoms, and psychological or socioeconomic issues that may impede adequate nutrient intake. Some experts recommend that people keep a daily diary of everything they eat, along with any dietary problems they encounter.

Once such an assessment is complete, promptly address any underlying

problems—such as infections, hormone imbalances, or metabolic disorders—that may be interfering with proper nutrition. The next step is to develop an appropriate, individualized nutrition plan. Seniors, growing children, pregnant or breast-feeding women, and people with active OIs are among the many groups that have special nutritional needs. While supplements can offer important benefits, they do not replace a well-balanced diet. When it comes to good nutrition, there is no “quick fix.” It’s better to develop long-term healthy eating habits, such as cutting back on saturated fat and consuming more fruits, vegetables, and whole grains. But set realistic goals: it’s fine to splurge occasionally if one normally adheres to a healthy diet. Fortunately, small changes in eating habits can often make a big difference in terms of health.

Since many people with HIV/AIDS use dietary supplements in addition to HAART, it’s crucial to learn more about how nutritional supplementation impacts HIV disease and vice versa. According to Tang and colleagues, areas ripe for further research include the role of micronutrient supplementation in people with well-controlled HIV disease, whether micronutrients can enhance CD4 cell responses, the role of antioxidants in countering increased oxidative stress due to HIV infection or its treatment, whether micronutrient supplementation can help reduce morbidity associated with coinfections such as hepatitis B or C, the role supplements might play in addressing metabolic manifestation such as lipodystrophy and bone loss, and the appropriate doses of supplements for HIV positive people at various stages of disease.

“Attempts to improve dietary quality and micronutrient status may play an overall role in maximizing health for the HIV-infected individual, particularly in undernourished populations,” Tang and colleagues concluded, “and may also play a role in

the more subtle management of HIV infection in the future.”

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# VITAMINS

NUTRIENT	ROLE IN HEALTH	GOOD SOURCES	COMMENTS
<b>Vitamin A</b> (retinol; pro-vitamin beta-carotene)	Eye, skin, bone, and epithelial cell health; proper digestive function; proper immune function, resistance to infection; normal red and white blood cell formation; tissue growth and repair; antioxidant (beta-carotene)	<b>Active form:</b> meat, liver, fish, cod liver oil, dairy products, eggs <b>Beta-carotene:</b> yellow, orange, and red vegetables and fruits (apricots, carrots, mangoes, red peppers, pumpkin, yams), dark green vegetables (broccoli, kale, spinach)	Fat-soluble—high doses can cause liver toxicity and leach calcium from bones; beta-carotene is converted as needed and less prone to overdose; large amounts may cause orange skin discoloration
<b>Vitamin B1</b> (thiamine)	Metabolism of nutrients; proper nervous system function and neuromuscular signaling; mental health (deficiency may cause irritability, depression); proper cell membrane function; may help reduce mitochondrial toxicity	Red meat, whole grains, legumes, peanuts, brewers yeast, wheat germ	B1 may be deficient in alcoholics; deficiency may cause peripheral neuropathy
<b>Vitamin B2</b> (riboflavin)	Eye, skin, and mouth health; metabolism of nutrients and release of energy; normal growth and development; proper nervous system function; mental health	Meat, liver, fish, eggs, dairy products, whole or enriched grain products, wheat germ, leafy green vegetables, mushrooms	Turns urine bright yellow-green
<b>Vitamin B3</b> (niacin)	Skin and mouth health; metabolism of nutrients; proper digestive function; proper nervous system function; mental health	Meat, poultry, fatty fish (salmon, tuna), whole grains, bran, legumes, peanuts	May cause flushing and sudden drop in blood pressure; used in higher doses to lower blood lipids and treat angina; may cause elevated blood sugar, liver toxicity
<b>Vitamin B5</b> (pantothenic acid)	Metabolism of nutrients; production of steroid hormones and neurotransmitters	Meat, poultry, fish, eggs, whole grains, legumes, soy products	Deficiency can cause burning foot pain
<b>Vitamin B6</b> (pyridoxine)	Skin and mouth health; normal red blood cell formation; absorption and metabolism of nutrients; proper nervous system function; mental health (deficiency may cause irritability, depression); proper immune function (cell-mediated immunity, antibody production); production of neurotransmitters	Meat, liver, poultry, fish, eggs, whole grains, legumes, nuts, seeds, leafy green vegetables, soy products, bananas	May cause nerve damage at high doses; administered with isoniazid to prevent depletion
<b>Vitamin B7</b> (biotin, vitamin H)	Skin, muscle, and red blood cell health; metabolism of nutrients; glucose metabolism	Synthesized by gut bacteria; organ meats, fish, eggs, cheese, wheat germ, brewers yeast, oatmeal, soy products, cauliflower	

## VITAMINS, continued

NUTRIENT	ROLE IN HEALTH	GOOD SOURCES	COMMENTS
<b>Vitamin B9 (folate/folacin/folic acid)</b>	Skin, mouth, and gastrointestinal health; metabolism of nutrients; proper nervous system function; synthesis of RNA and DNA; proper immune function; normal red and white blood cell formation	Leafy green vegetables, broccoli, citrus fruit, legumes, wheat germ, brewers yeast, whole and enriched grain products, sprouts, soy products	Helps prevent fetal neural tube defects when taken by pregnant women; may be deficient in alcoholics
<b>Vitamin B12 (cobalamin)</b>	Metabolism of nutrients; required for folate metabolism and use; proper nervous system function and neuromuscular signaling; mental health (deficiency may cause depression, cognitive impairment); proper immune function (including T-cell and natural killer cell activity); normal red blood cell function (deficiency can cause large cells with extra hemoglobin)	Synthesized by gut bacteria; red meat, organs meats, seafood, eggs, dairy products, soy products	Long-term vegetarians/vegans and alcoholics are at greatest risk for deficiency; some people are unable to absorb through the gut, so supplements may be administered by injection
<b>Vitamin C (ascorbate, ascorbic acid)</b>	Skin, mouth, eye, muscle, and blood vessel health; metabolism of nutrients; proper immune function, resistance to infection; wound healing (collagen synthesis); antioxidant	Citrus fruit, mangoes, kiwi fruit, peppers, tomatoes, cruciferous vegetables (cabbage, cauliflower, broccoli), berries	Vitamin C deficiency causes scurvy; high doses can cause diarrhea
<b>Vitamin D (cholecalciferol)</b>	Bone and teeth health; required for calcium and phosphate absorption and metabolism	Made by the skin when exposed to sunlight; fortified dairy products, fish liver oil, fatty fish (tuna, herring), eggs, wheat germ, nuts	Fat soluble; large doses may cause liver toxicity and calcium deposits in organs
<b>Vitamin E (tocopherol)</b>	Muscle, red blood cell, and cell membrane health; proper nervous system function; proper immune function (cell-mediated immunity); antioxidant	Vegetable oil, eggs, whole grains, wheat germ, nuts, soy products, avocados	Fat-soluble; fat malabsorption may cause deficiency
<b>Vitamin K</b>	Production of blood clotting factors (deficiency can cause excessive bleeding)	Synthesized by gut bacteria; liver, leafy green vegetables, cruciferous vegetables, whole grains, eggs	Fat-soluble; may build up in liver and can be toxic at high doses; liver disease may impair vitamin K use

## SELECTED MINERALS (not a complete list)

NUTRIENT	ROLE IN HEALTH	GOOD SOURCES	COMMENTS
<b>Calcium</b>	Bone and teeth health (deficiency may cause osteopenia, osteoporosis) enables absorption of calcium; proper nervous system function, nerve conduction, and neuromuscular signaling; proper heart function and blood clotting	Dairy products, canned fish with bones, soy products, nuts, leafy green vegetables, broccoli	Depleted by alcohol and caffeine
<b>Iron</b>	Enables red blood cells to carry oxygen (deficiency can cause anemia)	Red meat, liver, seafood, fortified grain products, leafy green vegetables, legumes, dried fruit, blackstrap molasses	May cause liver toxicity; promotes growth of bacteria and viruses; may promote free radical production; many experts recommend supplements without iron except for menstruating women
<b>Magnesium</b>	Muscle and heart health; metabolism of nutrients and release of energy; required for sodium, potassium, and calcium metabolism; proper nervous system function, nerve conduction, and neuromuscular signaling; mental health; normal growth and development	Leafy green vegetables, broccoli, whole grains, wheat bran, legumes, nuts, soy products, chocolate	
<b>Phosphate (form of phosphorous)</b>	Bone, teeth, and heart health; metabolism of nutrients; proper nervous system function, nerve conduction, and neuromuscular signaling; proper cell membrane function; maintenance of acid-base balance	Carbonated beverages, meat, poultry, fish, dairy products, eggs, legumes, nuts	High levels of phosphorous can impair calcium absorption, and vice versa
<b>Potassium</b>	Heart and muscle health; proper nervous system function, nerve conduction, and neuromuscular signaling; maintenance of fluid balance and cellular homeostasis	Bananas, figs, leafy green vegetables, broccoli, citrus fruits, peanuts, seeds	Deficiency can result from prolonged vomiting or diarrhea
<b>Selenium</b>	Heart and red blood cell health; proper immune function (including white blood cell activity); normal growth and development; antioxidant	Brazil nuts, cashews, red meat, organ meats, seafood, dairy products, whole grains, legumes, seeds	Deficiency is most likely in areas where soil is low in selenium
<b>Zinc</b>	Proper immune function (cell-mediated immunity, antibody production) cell division, growth, and repair; wound healing; proper cell membrane function; proper nervous system function; mental health; antioxidant	Meat, poultry, seafood, dairy products, eggs, whole grains, brewers yeast, legumes, seeds	Deficiency may cause alterations in senses of taste and smell

# Aging with HIV

Sharon  
Lee

Several of the physical symptoms and illnesses related to HIV disease and its treatment—such as fatigue, weight changes, memory loss, depression, and atherosclerosis—mimic typical age-related health problems. It is estimated that at least 10% of HIV positive people in the United States are 50 years of age or older—a number that will certainly increase as people with HIV live longer thanks to effective antiretroviral therapy. For older women, sorting out the interplay between HIV, aging, and the side effects of medications can be very difficult. Many health problems are exacerbated by smoking, obesity, and poor health behaviors that can lead to an increased risk of illness or death. This article addresses two common health risks in aging women with HIV: heart disease and osteoporosis.

## Heart Disease

Though many people tend to think of cardiovascular disease as an affliction of older men, coronary heart disease is the leading cause of death for women in the U.S. Over 30% of deaths among women are due to heart attacks, while another 8% are due to strokes. While one in 25 women will eventually die of breast cancer, one in *two* will eventually die of heart disease or stroke.

But not all women are at equal risk. African-American women, for example, are twice as likely as white women to develop heart disease, which is thought to be related to a higher incidence of high blood pressure, diabetes, and obesity among this group. For all women, both heart attacks and strokes are strongly associated with smoking, high blood pressure, elevated blood lipid (fat) levels, diabetes, poor diet, and lack of exercise. Fortunately, many of these risks can be reduced by adopting a healthier lifestyle.

Are women with HIV at greater risk for developing heart disease than HIV negative women? It is still uncertain just how much HIV or its treatment may increase the risk of heart attack and stroke. A growing number of studies have attempted to evaluate how HIV and/or antiretroviral medications affect cardiovascular disease, but much of this research has failed to produce definitive answers. Research has yielded conflicting results, which is not surprising due to the difficulty of sorting out all the overlapping

factors that affect both heart disease and HIV (see “Cardiovascular Disease in People with HIV,” in the Summer/Autumn 2002 issue of *BETA*). For example, we know that some of the traditional risk factors for cardiovascular disease—such as elevated cholesterol and triglycerides—are more common in people with HIV. These metabolic changes may, in fact, turn out to be associated with highly active antiretroviral therapy (HAART), yet undoubtedly the benefits of taking medicines that help control HIV are well documented. On the other hand, a behavior such as smoking is clearly associated with a greater risk of heart disease and has no health benefits.

Long-term studies comparing similar populations of women with and without HIV are helping to sort out some important issues. The ongoing Women’s Interagency HIV Study (WIHS), established in 1993 to investigate the impact of HIV infection on women in the U.S., has conducted the most targeted study to date regarding women, HIV, and cardiovascular disease. This study examined the occurrence of heart problems in three groups: HIV positive women taking HAART, HIV positive women who chose not to take HAART, and HIV negative women who were matched for socioeconomic and behavioral characteristics. More than 1,500 women were evaluated. The findings indicated that the primary associated risks for heart disease were smoking and increasing age—not HIV disease—

**Particularly in patients with advanced HIV disease, it is clear that the immediate benefits of HAART far outweigh the risks of cardiac disease.**

regardless of whether or not the women were taking anti-retroviral medications.

Smoking cessation and controlling hypertension and diabetes are by far the most important factors in attaining good cardiovascular health. Particularly in patients with advanced HIV disease, it is clear that the immediate benefits of HAART far outweigh the risks of cardiac disease.

### *Osteoporosis*

Bone is a dynamic material that is continuously remodeled through rebuilding and resorption of the calcium matrix. When an imbalance occurs in this process—causing greater resorption than deposition of calcium—the result is a weakening of the bone. Postmenopausal women are much more likely to experience bone thinning or loss of calcium from the bones, a condition called osteopenia (mild to moderate bone loss) or osteoporosis (more severe bone loss). Osteoporosis can lead to curvature of the spine and increased risk of fractures. (For more information, see “Osteoporosis,” in the Summer/Autumn 2001 issue of *BETA*.)

Osteoporosis occurs most often in women over the age of 50. Factors such as low body weight, smoking, lack of exercise, inadequate calcium intake, heavy alcohol consumption, and certain medical conditions including kidney or liver failure, previous thyroid surgery, asthma, and chronic lung disease increase the risk of osteoporosis. The condition may also be worsened by the use of some medications, such as heparin, antiseizure drugs, and prednisone. Studies on the effects of HIV and HAART on bone loss have produced conflicting results. Some indicate that HAART exacerbates bone loss, while others suggest that it has little or no effect.

One study, conducted by Sara Dolan, NP, and colleagues from Harvard Medical School, found that the prevalence of osteopenia was 2.5 times greater in HIV positive women than in HIV negative women, and that the use of antiretroviral therapy did not lower or increase their risk. Other risk factors for bone loss included low body mass index, a history of low body weight, low body fat percentage, and infrequent menstruation. Additionally, the pattern of bone loss in HIV positive women differed from that seen in postmenopausal HIV negative women, with different blood markers of bone metabolism and a shift in the balance between bone formation and resorption. In another WIHS study, Kathryn Anastos, MD, and colleagues measured bone mineral density in 88 HIV negative and 184 HIV positive women (of whom 94 were taking HAART and 90 were not). The prevalence of osteopenia/osteoporosis was 6.4% in the HIV negative women, 18.9% in the HIV positive women not on HAART, and 20.4% in the HIV positive women receiving HAART. This study, too, indicated that HIV infection increases the risk of osteoporosis, regardless of whether or not antiretroviral medications are used.

Several other studies, however, have found that some of the medications used in HAART combination regimens may increase the rate of bone loss. To complicate the issue further, research at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) suggested that some anti-HIV drugs may actually preserve bone by slowing resorption of calcium. Therefore, it is difficult to draw definitive conclusions from this research other than that the process of bone resorption and deposition is affected by many factors, including HIV and its treatment.

One thing that is clear is that it is possible to reduce the risk of developing osteoporosis through regular weight-bearing exercise such as walking, adequate dietary calcium intake (along with vitamin D), and avoiding smoking or excess alcohol use. Most experts believe that standard medications approved for the treatment and prevention of osteoporosis are appropriate for women with HIV, though as yet there have been no studies to show whether these medications have the same results for HIV positive and HIV negative women. However, a few small studies that included mostly men have found that alendronate

### **Good health behaviors are important for everyone to help prevent heart disease and strokes. Here are a few things you can do to reduce your risk:**

- Quit smoking. Talk with your healthcare provider if you need help.
- Eat a well-balanced, low-fat diet. Cut back on foods high in saturated fat and cholesterol.
- Check your blood pressure, cholesterol, and blood sugar levels regularly, and keep them under control.
- Exercise regularly. Exercise does not need to be strenuous; walking, climbing stairs, and other kinds of aerobic exercise have long-term health benefits.
- Lose weight if you are overweight or stay at a healthy weight.

(Fosamax) plus calcium and vitamin D improved bone loss in people with HIV.

One of the greatest perils of osteoporosis is an increased risk of fractures due to falls. Elderly women and HIV positive women may be more likely to experience falls because of medication side effects and/or neuropathy (which can interfere with sensation in the feet and lower legs). For this reason, it is important to reduce the risk of falls in the home. Removing throw rugs and other hazards, using nonskid bath mats and tub handrails, and wearing shoes with nonskid soles are important measures to prevent broken bones.

## Conclusion

In addition to heart disease and bone loss, older women with HIV may experience other age-related problems, including arthritis, difficult menopausal symptoms, and cognitive impairment. While many older people with HIV were infected decades ago, others acquire the virus later in life. Unfortunately, many older individuals do not perceive themselves as being at risk for HIV infection—therefore neglecting to practice safer sex or get tested for the virus—and their healthcare providers may fail to consider HIV as a potential cause of illness. The good news is that older people with HIV appear to respond as well to antiretroviral therapy as their younger counterparts.

Arthritis, which affects nearly 70 million people in the United States, may be caused by a variety of factors, including autoimmune reactions and wear and tear due to aging. To date, research has not shown how arthritis is affected by HIV or its treatment.

Some experts have suggested that women with HIV may experience earlier menopause and more severe menopausal symptoms than HIV negative women. But many such anecdotal reports come from the pre-HAART era, when severe illness and wasting were more common. Controlled studies of menstrual irregularities and hormonal abnormalities in HIV positive women have yielded inconsistent results (see “HIV and Hormones,” in the Summer 2004 issue of *BETA*). In the November 15, 2005 issue of *Clinical Infectious Diseases*, Ellie Schoenbaum, MD, and colleagues reported on a study of menopause in 571 HIV positive and HIV negative women. They concluded that HIV infection and immunosuppression were associated with an earlier onset of menopause, but noted that more research is needed to determine whether early menopause puts HIV positive women at greater risk for osteoporosis and heart disease. Because studies have not yet clarified the risks and benefits of hormone replacement therapy in this population, HIV positive women should consult their doctors for individualized recommendations.

While it is clear that HIV affects the brain, “few studies have investigated the complex interactions between HIV infection, aging, and neuropsychiatric diseases,” according to Nathalie Casau of the Albert Einstein College of Medicine, whose review of HIV and aging appeared in the September 15, 2005 issue of *Clinical Infectious Diseases*.

Compared with the early years of the epidemic, people with HIV are now much more likely to live well into their senior years, and many are experiencing age-related conditions they never expected to face. As such, there is an increasing need for research on how HIV disease impacts—and is impacted by—common conditions associated with aging. Much also remains to be learned about how aging affects the immune system. Further, there is a growing need for healthcare providers treating HIV positive people to integrate geriatric concerns into their practices. But one thing is certain: healthy habits are associated with longer life expectancy and improved quality of life for people of all ages.

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# Dual HIV Infection

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A number of individuals infected with more than one strain of HIV have been identified over the past few years. Should people already diagnosed with HIV be concerned? Given the limited number of cases seen so far, the risk of multiple infections (also called dual infection) appears to be quite low. And there are many more pressing health concerns facing people living with HIV/AIDS. Nevertheless, two trends are worth noting: dual infection seems more likely to happen under certain conditions, and it is associated with faster progression to AIDS-related events. This article describes current evidence and theories behind this emerging phenomenon.

## COINFECTION AND REINFECTION

Researchers make a distinction between two types of dual, or multiple, HIV infection:

**Coinfection**, or infection with more than one viral strain at or near the same time, is believed to occur around the time of initial infection. (Initial infection is also known as acute or primary infection—the period before seroconversion that usually lasts from a few weeks to a few months.)

**Reinfection** with a different strain, also known as *superinfection* or *serial infection*, presumably takes place later on during early infection (the first few years of HIV disease, after seroconversion) or chronic (long-term) infection.

In theory, any apparent case of reinfection could be a case of coinfection in which one of the coinfecting strains remains undetectable until it emerges sometime after seroconversion (the point at which HIV antibodies can be detected and a person can be diagnosed as being HIV positive). This is sometimes called sequentially expressed coinfection. Testing limitations that prevent detection of very small viral populations in the body make it difficult to distinguish between coinfection and reinfection. Researchers believe that until a source partner for dual infection is found and the timing of exposure confirmed, it is not possible to determine that the second virus was acquired after seroconversion.

While finding source partners is a continual problem, determining the timing of exposure is aided in some cases by the emergence of acute retroviral syndrome (often flu-like symptoms, including fever and fatigue) in the person presumed to be reinfected. It is not known whether overgrowth of a previously dormant coinfecting strain might also trigger acute retroviral syndrome.

## Gathering Evidence

Experts once hoped that a single HIV infection would prevent further infections, much like a vaccination. In the mid-1990s, however, studies using analogous viruses in primates showed that sequential infections were possible. Some people believed it was only a matter of time before something similar would be seen in humans.

Compelling evidence of dual HIV infection in humans appeared in 2002. A report in the *Journal of Virology* in August of that year strongly suggested reinfection in two injection drug users (IDUs) from Thailand (one female, one male). The woman was initially diagnosed with HIV subtype AE only, followed by detection of subtype B approximately two months later. The man was apparently reinfected with subtype AE virus approximately six to ten months after his primary diagnosis with subtype B virus. Neither individual was being treated for HIV during the study period.

In the September 5, 2002 issue of the *New England Journal of Medicine*, researchers from the University of Geneva reported on a man initially diagnosed with subtype AE virus in November 1998 whose viral load became undetectable (below 50 copies/mL) with antiretroviral therapy. He stopped treatment in January 2001 and shortly thereafter traveled to

## HIV Recombination

Different varieties, or strains, of HIV are grouped in a hierarchy. At the broadest level are the two types of HIV: **HIV-1** (most prevalent worldwide) and **HIV-2** (rare except in West Africa). HIV-1 is divided into three groups: **M** (major), **N** (new), and **O** (outlier). Group M is by far the most common of the three, and is itself subdivided into different clades or subtypes: **A–D, F, G, H, J, and K**.

Different subtypes can infect a cell and create hybrid or recombinant forms, such as AC (or A/C). Circulating recombinant forms, or CRFs, are genetically mixed subtypes (such as CRF02\_AG) that are found in more than one person.

Types	HIV-1	HIV-2
Groups	M — N — O	
Subtypes (Clades)	A B C D [E]* F G H J K	
	recombinant forms and CRFs	

*\* E does not exist on its own, although it appears in certain CRFs*

Most recombination events seen thus far are between different subtypes. But infection with two genetically distinct viruses of the same subtype—for example, two subtype B viruses—is also possible. The potential for recombination among these is unknown.

At the same time, science has yet to reveal what might result from viral mixing among different HIV groups or types. But research opportunities might come soon. At the 2005 Retrovirus conference, a French team claimed to have detected the first reinfection of a group O-infected woman with a virus from group M. Almost more remarkably, the research group located the source of her second infection, the gold standard for confirming secondary infection that has eluded other investigators.

While it is generally believed that dual infection must occur for a recombinant virus to be formed, an unusual case of viral recombination in a singly infected woman was reported at the 3<sup>rd</sup> IAS conference this past July. B. Weiser of the New York State Department of Health and colleagues found that this individual's drug-sensitive HIV evolved differently in her plasma and genital tract after starting HAART and recombined into a multidrug-resistant strain within six months.

Brazil, where he had multiple unprotected sexual contacts. In April 2001, three weeks after his return from South America, his viral load spiked to 400,000 copies/mL and he reported symptoms of acute retroviral syndrome, which can signal a new HIV infection. Lab tests subsequently

detected a second strain of HIV—subtype B, which is common in Brazil. The researchers concluded that reinfection had occurred.

More recently, Davey Smith, MD, of the University of California at San Diego and colleagues reported in the August 12, 2005 issue of *AIDS* that a

man with wild-type (drug-sensitive) subtype B virus was apparently reinfected about a year after his first infection with a different subtype B virus resistant to protease inhibitors, which he had never taken, and 3TC (lamivudine, Epivir), which he started only after the second infection. Another case of dual infection with two subtype B viruses with discordant drug sensitivity was reported by the same research group in 2003. In that case, however, the subject was first diagnosed with drug-resistant subtype B virus and then found to have wild-type HIV of the same subtype four months later. Like the man in the 2005 report, this individual had not taken antiretroviral therapy before the apparent reinfection event.

Other cases of multiple HIV infection have been identified in the past four years, although the total number remains small—only 16 apparent reinfections by one measure (a 2005 Medscape survey of the scientific literature done by a group from the Gladstone Institute of Virology and Immunology in San Francisco). The Gladstone researchers, however, did not consider cases of coinfection. In addition, dual infection rates may be higher than reported, since few people with HIV have been tested for multiple strains. Only larger future studies using more sophisticated technologies and better tracking of source partners can provide a clearer picture of the incidence (rate of new cases) and prevalence (total number of existing cases) of coinfection and reinfection in a given population.

## Impact on Disease Progression

Dual infection in humans has been linked to disturbances in immune control and poorer prognosis. In the case of the man who traveled to Brazil, the emergence of his subtype B virus while off therapy coincided with a loss of 300 CD4 cells/mm<sup>3</sup> and a dramatic rebound in viral load before he resumed highly active antiretroviral therapy (HAART) four months later.

In a report from 2004, Smith and colleagues analyzed the two dual infection cases mentioned above plus a third man with apparent secondary infection (wild-type followed by drug-resistant virus). Among the three men, CD4 cell counts dropped an average of 132 cells/mm<sup>3</sup> within six months of acquiring the second strain, while viral load levels increased an average of 1.6 logs—a 40-fold increase.

Geoffrey Gottlieb, MD, of the University of Washington in Seattle and colleagues retrospectively located five individuals with dual infection (four U.S. gay men, one female sex worker from South Africa). Four were coinfecting near the time of seroconversion, while the other was reinfected 1.3 years after initial infection. All five had rapid disease progression: from seroconversion to below 200 CD4 cells/mm<sup>3</sup> within 3.1 years on average, and to an AIDS diagnosis or death within 3.4 years. Time from seroconversion to AIDS typically takes 8–10 years in untreated individuals.

In a letter to *The Lancet* in June 2005, Gottlieb proposed that the case of unusually rapid HIV disease progression in a New York City man described by local health officials in February 2005 might also be due to dual infection rather than the emergence of a so-called “supervirus” (see “News Briefs” on page 4).

Several factors might explain an association between dual infection and a surge in HIV disease progression. For now, these are hypothetical and could be related to viral dynamics and the way the second virus attacks the immune system or evades immune responses.

Acquiring a drug-resistant viral strain, for instance, would increase the likelihood of losing a response to antiretroviral therapy. This was seen in Smith’s 2005 report as well as others. For those not on treatment, overwhelming a drug-resistant virus (considered less able to replicate) with a new wild-type virus (considered more virulent) could result in a higher viral load and speed progression of disease.

Viral recombination might play a significant role in accelerating HIV disease (see sidebar on page 37). Recombination increases viral diversity more rapidly than mutations that evolve slowly through replication errors. Recombinant viruses may be less sensitive to anti-HIV drugs and are potentially more virulent than nonrecombinant viruses. This might result from altered tropism—specifically, the virus’ ability to use the CXCR4 coreceptor to enter cells, as was the case in the New York man; CXCR4-using viruses are associated with worse disease outcomes than viruses that use the CCR5 coreceptor.

Genetically mixed viruses might also be more adept at evading immune responses in a type of evolutionary strategy. At the 3<sup>rd</sup> International AIDS Society (IAS) conference this past July, Carolyn Williamson, PhD, from the University of Cape Town and colleagues reported finding recombinant virus in six of six dually infected subjects, along with evidence of viral evasion of cellular immune defenses and neutralizing antibodies. The South African team proposed that dual infection “enables recombination to contribute significantly to viral adaptation to immune responses...and may help explain rapid disease progression.”

Alternatively, the link between dual infection and disease progression might be a product of individual characteristics. Gottlieb has speculated about whether certain people who are inherently predisposed to faster disease progression may also be more susceptible to reinfection. His team noted in their 2004 report, for example, that the one subject believed to be reinfected “had rapid CD4 decline immediately after initial infection, suggesting a host susceptibility to infection with a second virus.”

## Susceptibility and Protection

As to when reinfection might occur, data collected so far show an interesting trend. Researchers at the Gladstone Institute pointed out in

their survey of the literature that multiple infections have not been reported in anyone beyond three years after his or her first infection. (Only a female sex worker from Kenya with recombinant AC virus might have been reinfected after three years, but the exact date is unknown due to a nine-year gap in blood sampling.) This observation has been borne out in recent studies in which dual infection was not observed in chronically infected individuals, even among IDUs who consistently shared needles and HIV positive individuals who had partners with different strains and high risk of re-exposure.

While this trend may be an inaccurate observation based on coincidence or testing errors, it has also been seen in primates. A study done in the late 1990s by Ron Otten, PhD, and colleagues from the Centers for Disease Control and Prevention (CDC) showed that macaque monkeys could be infected with two strains of HIV-2 up to four weeks after a first infection, but not between eight and 72 weeks afterwards. Humans might have a similar window of susceptibility to reinfection of approximately three years.

The lack of evidence for dual infection during chronic (long-term) HIV disease suggests a protective mechanism at work, such as immune responses that evolve over time or “viral interference”—the ability of the original virus to ward off acquisition of another. Any protective role played by anti-HIV therapy in chronic infection would appear to be negligible, since multiple infections have not been reported in untreated chronically infected people after three years.

Dual infection therefore seems to occur only during acute or early infection—and in these cases, anti-HIV therapy might well make a difference. Evidence suggests that multiple infections happen only in people with acute or early infection who are not being treated or only intermittently treated with anti-HIV drugs. This implies that antiretroviral therapy has

a protective effect, at least during early HIV disease, either in blocking secondary infections or in preventing certain coinfecting strains from asserting themselves. Antiretroviral agents used as pre-exposure prophylaxis (PREP), taken before a high-risk incident, might work in a similar way to block a first infection. However, using anti-HIV agents as PREP remains experimental and unproven.

Although continuous antiretroviral therapy (during early disease) and chronic infection (regardless of treatment) each appear to provide protection against dual infection, more research is needed to understand and confirm these observations. Studies are likewise needed to identify any individual characteristics that might make some people more prone to acquiring a second virus. These factors are currently unknown, although cases such as the one described by Gottlieb in 2004 point to the possibility.

## Managing Dual Infection

The appearance of genetically distinct viruses within an individual complicates the management of HIV disease. Because multiple infections often lead to signs of accelerated disease progression, the typical clinical response has been to begin or resume anti-HIV treatment. Some people among the recently documented cases have controlled their secondary infection with standard antiretroviral therapy. Others, even if responding well to a first regimen before reinfection, have required salvage or rescue regimens containing four or more drugs. Resistance tests may help guide clinicians in their choice of therapy. Newer drugs and drug classes might likewise improve the chances of treatment success, especially in cases of secondary infection with a drug-resistant virus.

The current understanding of dual infection raises complex questions for people with HIV, clinicians, and prevention workers alike. What approach, if any, should be taken

given the small number of cases? Should people with early HIV disease be counseled to start treatment to avoid reinfection, even if their virus is under control? What impact will reinfection have on HIV positive individuals who “serosort,” or choose to have sex only with other positive people? Will those with chronic infection feel freer to have unprotected sex despite the risk of acquiring other sexually transmitted infections (STIs)?

As always, the best guide to risk management is reliable information. The Gladstone researchers wisely counsel that “clinicians and researchers should provide balanced and broad views of the risks of unprotected sex between HIV-1 infected persons, and avoid exaggerated or sensational claims about superinfection that could undermine behaviors such as serosorting and serodisclosure that can help to curtail the spread of HIV.” Beliefs about multiple infections can affect behavior. In interviews with 193 HIV positive men who have sex with men (33% Latino, 29% African American), researchers from the San Francisco Department of Public Health reported in 2003 that the 83% who believed reinfection was damaging to health were significantly less likely to report unprotected anal sex with an HIV positive partner or any partner compared with those who did not share this belief.

## Vaccine Design

Recent dual infection news has been sobering for vaccine researchers, who study the mechanisms the immune system uses to control pathogens (disease-causing organisms) and work to develop agents that will elicit the same immune responses. The specific protective mechanisms, or “correlates of protection,” necessary to subdue HIV are unknown, which has been a major obstacle in HIV vaccine research since the beginning of the epidemic. The task is now made more difficult by the knowledge that the immune system cannot reliably prevent reinfection

even when responding vigorously to an initial infection.

At the 2003 Retrovirus conference, for example, Todd Allen, PhD, of Massachusetts General Hospital and colleagues reported that a robust and specific immune response to one HIV subtype (B) did not inhibit reinfection with another. The fact that virus-specific immune responses are unable to stop other invading viruses—even those of the same subtype, as seen in the cases reported by Smith’s group—suggests that priming the immune system with a vaccine to control one viral subtype will not be sufficient, and that designing a vaccine broadly protective against a range of HIV strains might be impossible.

Still, with the added challenge comes a silver lining: the apparent protection afforded by chronic infection, antiretroviral drugs, or individual characteristics. Figuring out how these or other factors allow the immune system to prevent dual infection could be a significant breakthrough and may help guide researchers toward their elusive goal. Given the moribund state of HIV vaccine development, no time should be wasted in exploring this possibility.

## Conclusion

What little is known about dual infection has been sketched from a handful of case reports. Uncertainty will prevail until scientists resolve the issue of whether reinfection occurs independently of coinfection. If all dual infections are in fact coinfections acquired at or near the same time, there would theoretically be no risk of later being reinfected with a second strain of HIV. Studies would then focus on why, when, and in whom coinfection takes place, as well as why some coinfecting HIV strains emerge virulently and only during early infection.

If, however, reinfection is a distinct phenomenon, researchers will need to determine precisely what conditions are necessary for multiple infections to occur, who might be

more susceptible to them, and what are the clinical implications. Only a fuller understanding of dual infection can help people with HIV make informed decisions about risk. (For information about the Positive Partners study, which looks at whether reinfection occurs between sexual partners, see “Open Clinical Trials” on page 54.) And, with luck, investigating the dynamics of multiple infections might lead to the ultimate protection: an HIV vaccine.

**Nicholas Cheonis is the former editor of *BETA*.**

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## **Having Problems with Medicare Part D Prescription Drug Coverage?**

The new Medicare Prescription Drug Benefit, Part D, began on January 1, 2006, and affects all 60,000–80,000 individuals with AIDS across the country who receive Medicare coverage.

In the first weeks of the new program, Part D beneficiaries have already experienced a number of significant problems accessing their medications. These problems include individuals being asked to pay higher co-pays than they should, not being automatically enrolled in a plan, or being told they had no Part D coverage when they had in fact signed up.

The San Francisco AIDS Foundation and Project Inform encourage individuals who are continuing to experience difficulties with Part D to let us know—we can help you resolve these problems, and your story will help us advocate to improve the program. We can be contacted by email at [dvangord@sfa.org](mailto:dvangord@sfa.org) or [adonnelly@projectinform.org](mailto:adonnelly@projectinform.org).

“Medicare Prescription Coverage” in the Summer 2005 issue of *BETA* explains Part D at length. We encourage you to refer to this article and to check the AIDS Foundation and Project Inform websites for regularly updated information about the new program at [www.sfa.org/policy/medicare](http://www.sfa.org/policy/medicare) and [www.projectinform.org](http://www.projectinform.org).

# A Guide to Clinical Trials

CBC (INCLUDES DIFF/PLT)	
WHITE BLOOD CELL COUNT	4.8-10.8
RED BLOOD CELL COUNT	4.2-5.9
HEMOGLOBIN	12-16
HEMATOCRIT	37-47
MCV	86-106
MCH	31-36

THOUS/MCL	3.8-10.8
BILL/MCL	4.20-5.80
	13.2-17.1
	38.5-50.0
FL	80.0-100.0
	8-33.0

## PART II: INTERPRETING MEDICAL RESEARCH

*Part I of this two-part article, which appeared in the Summer 2005 issue of BETA, provided an overview of the clinical trial process. Part II covers features of clinical trials and interpretation of study results.*

Clinical trials provide the foundation for evidence-based medicine, or medical decision-making guided by data from formal research. Medical professionals keep up with the latest information by reading peer-reviewed medical journals and attending conferences. Likewise, HIV positive people can keep abreast of the state of the art by following the medical literature and community publications like *BETA*.

Trials offer important information about a therapy's benefits and risks in a population, but they cannot predict how well a given treatment will work for a specific person. Healthcare providers, therefore, must still rely heavily on clinical experience, intuition, and a careful evaluation of the various factors unique to each individual case—the practice of medicine remains an art as well as a science.



13.4  
183  
2129  
1236  
456  
51  
27  
54  
31  
1  
0

32.0-36.0
11.0-15.0
140-400
1500-7800
850-3900
200-950
10-300
0-20



HIV-1 RNA, Q
hdNA, 3RD
COPIES/ML

## Characteristics of Medical Research

In the hierarchy of medical research, some types of studies are regarded as more credible than others. Research is considered most valid when it focuses on events in progress rather than those that have already occurred, includes enough participants observed over a long enough period so that the results are **statistically significant** (not likely to be due to chance alone), and takes steps to reduce the influence of confounding factors and minimize bias on the part of investigators and subjects.

### Retrospective vs Prospective Studies

Retrospective studies look back at events that happened in the past, often using medical records. In **prospective studies**, a group of subjects is selected and followed forward in time. Retrospective studies are considered less reliable because it is more difficult to control (or even recognize) potential confounding factors when looking at past events. For example, it would not be very useful to compare the results from a recent study of atazanavir (Reyataz) with data from an early-1990s trial of a first-generation protease inhibitor such as indinavir (Crixivan), because both the nature of HIV disease and the standard of care have changed so much in the intervening decade.

In addition, important pieces of information may be unavailable when looking back over time. For instance, medical records dating back to the early years of the epidemic would not include HIV viral load measurements, since this test was not widely used until the mid-1990s.

### Study Size and Length

Other factors being equal, longer trials with larger **sample sizes**—that is, more participants—are considered more reliable than shorter studies with fewer subjects. Longer and larger trials produce more data, making it less likely that the observed outcome is simply due to chance. The ability of a

study to produce statistically significant results is known as its **power**.

A report of the natural history of a disease and its treatment in a specific individual or a small group of patients is called a **case report** or a **case series**, respectively. Case reports often describe exceptional or unusual events and have the benefit of speed; as such, they may uncover uncommon side effects (such as heart problems associated with protease inhibitors) before they are revealed in clinical trials. This type of **anecdotal evidence** may be interesting, but is not considered conclusive because it is impossible to know how individual factors may have influenced the observed events.

**Case-control studies** provide an additional level of reliability. In these studies, each person with the variable under study (a case) is matched with one or more individuals with otherwise similar characteristics (a control). This matching makes it easier to discern the effect of a particular variable by ensuring that cases and controls are alike in other respects.

In a **cohort study**, a group of individuals with shared characteristics is selected and followed forward in time, typically for many years. The HIV Outpatient Study (HOPS), the Multicenter AIDS Cohort Study (MACS), the Women's Interagency HIV Study (WIHS), and the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study are all examples of cohort studies looking at various populations with HIV/AIDS. In this type of study, researchers do not perform a specific intervention (such as administering a particular drug), but rather observe the effect of various factors (e.g., demographic characteristics, type of therapy, hepatitis C coinfection) on the natural history of the disease over time.

**Clinical trials** are carefully planned studies looking at particular therapeutic interventions. The process proceeds in phases, with each successive stage lasting longer and including

more subjects (this is covered in “Part I: Understanding Clinical Studies”). This is done to achieve a trade-off of safety and credibility. Only small numbers of participants are exposed to potentially risky new agents during Phase I trials. After a drug is shown to be generally safe, large numbers of subjects are included in Phase III trials to obtain more reliable data on **efficacy** (how well it works).

Once several studies have been done looking at a particular therapy, researchers may conduct a **systematic review** (comprehensive overview of related studies) or a **meta-analysis** (mathematical analysis that incorporates data from multiple studies). These secondary studies provide a “big picture” summary of information amassed so far. If several well-designed trials produce similar results, confidence in the outcome is enhanced.

### Controlled Studies

Clinical trials with large sample sizes and long follow-up periods provide stronger evidence than single case reports or case-control studies, but may still leave room for **bias** (“favoritism” or “prejudice” that skews an outcome in a systematic way) and **confounding factors** (extraneous variables that can distort a trial's outcome).

Various strategies are employed to minimize conscious or unconscious influences that could unfairly affect a trial's results. The “gold standard” for research on medical interventions is the prospective, **double-blind**, randomized, controlled trial. Briefly, *double-blind* means that neither the investigators nor the subjects know who is receiving the experimental agent. **Randomization** refers to the process of assigning subjects by chance to the various treatment arms. This is done to help ensure that at the outset of the trial the subjects in the various arms are comparable, or as similar as possible in every respect except for the type of intervention they are receiving. A **controlled trial** is one in which the experimental

agent is compared against something else, either a placebo (inactive or mock therapy) or an existing effective treatment (these characteristics are described in more detail in Part I).

## Statistics 101

Investigators are not always able to design and implement randomized controlled trials to test every hypothesis. For instance, it would be unethical to randomly assign HIV positive pregnant women either to give birth vaginally or undergo a cesarean section (c-section) to see which method results in a lower rate of mother-to-child HIV transmission. The best researchers can do is compare the HIV status of infants who happened to be born vaginally or through c-section, but these groups might differ in other ways (e.g., perhaps women who had c-sections were less likely to have received prenatal care).

Fortunately, researchers can use various statistical methods to make adjustments for systematic (consistent and predictable) differences between groups of subjects. For example, it is a common finding that individuals coinfect with HIV and hepatitis C virus (HCV) are more likely to be injection drug users and tend to be younger than people with HIV alone. It is also known that HCV-related liver damage increases with age and that older individuals tend to respond less well to interferon-based therapy. Therefore, investigators must adjust for the subjects' age if they are attempting to determine whether coinfection is associated with liver disease progression or response to anti-HCV treatment. Investigators can also **stratify** their data to look separately at subgroups with different confounding characteristics.

Another statistical concern related to clinical studies—especially those that include representative “real world” populations—is that raw data are rarely “clean,” or free of potentially confounding influences. Investigators often must take multiple coexisting factors into account. Looking again at hepatitis C, it is known that, along

with older individuals, men tend to respond less well to interferon than women, and African-Americans respond less well than whites. Thus, researchers looking at the relative benefits of two different interferon-based regimens would need to use mathematical models that account for how all these variables interact to influence the observed outcome. It is not uncommon that a factor that initially seems important in a **univariate** analysis that looks at a single variable alone will no longer appear relevant when a **multivariate** analysis is performed to account for multiple interacting variables.

## Statistical Significance

As noted above, study results are considered statistically significant if there is little likelihood that the observed outcome was due to chance alone. When looking at data from different arms of an interventional clinical trial, researchers attempt to determine whether the **null hypothesis**—the assumption that the various interventions are equally effective—is true or false.

Researchers use the **P value** to indicate the probability that an observed result is true and not just due to happenstance (for example, that an experimental agent really works, not just that more of the subjects who took it had the good luck to improve). While studies may use different cut-off values, a P value below 0.05 ( $p < 0.05$ ) is traditionally accepted as an indication of statistical significance. This means that the likelihood is less than 5%, or 1 in 20, that the observed difference between study arms was simply due to chance. Smaller P values indicate even greater certainty. A P value below 0.01 ( $p < 0.01$ )—considered “highly statistically significant”—means that there is less than a 1% probability that the observed outcome would have occurred by chance alone.

While the P value provides a single cut-off for statistical significance, the **confidence interval** (CI) provides a range within which the true result is

likely to fall. Researchers traditionally use a 95% CI, meaning that there is a 95% likelihood that the actual difference lies within this range. Studies with higher power (e.g., more subjects) typically produce narrower confidence intervals, meaning researchers can feel more certain about the accuracy of their results. The actual values included in a CI also convey useful information. In an interventional trial, if the null hypothesis were true, the difference between two treatments under study (or treatment and placebo) would be zero. Thus, if a CI includes zero, researchers cannot rule out the possibility that the interventions were equally effective. In trials looking at risk factors for a condition, a **relative risk** or **odds ratio** (OR) of 1 means that a factor had no effect; in this case, if a CI includes 1, researchers cannot rule out the possibility that the risk factor had no impact on the condition's occurrence.

## Interpreting Significance

All studies yield a certain level of **false positive** and **false negative** data. For instance, an experimental drug may seem to work for a particular subject even though it is, in fact, ineffective overall; conversely, an agent may not help a specific subject even though it is effective overall. The goal in a well-designed study is for these types of subject-specific variability to cancel each other out, so that any actual benefit of an intervention will become apparent. Failure to detect a true difference between interventions is known as a **type II** error, while erroneously finding a difference between two interventions that are in fact equally effective is called a **type I** error.

If the difference between study arms is statistically significant—that is, the P value is larger than the chosen cut-off value and/or the CI does not include zero—the investigators can be reasonably confident that the null hypothesis is false and that one intervention really is superior to another. In real world terms, if the

## The “gold standard” for the presentation of medical research is publication in a peer-reviewed professional journal.

observed difference in HIV viral load suppression between two study arms receiving two different drug regimens is statistically significant, this suggests that one regimen really does work better.

If the observed difference is not statistically significant, it could be that the two regimens have about the same efficacy (or lack thereof). But it could also mean that the study was **underpowered** or too small to demonstrate an effect. Larger and longer-lasting studies—those with higher power—are more likely to produce significant results. Studies with low power produce wide CIs, meaning the true result could lie within a broad range. Statistical tools are available to help investigators determine in advance how large a sample size they will need to detect a true difference between study groups.

### Reporting Study Results

After a clinical trial is completed, investigators typically present their research results to their colleagues. The two main venues for disseminating data from medical research are scientific meetings and professional journals.

### Scientific Conferences

Often researchers first publicly present their findings at conferences devoted to their fields of study. Important HIV/AIDS meetings include the Conference on Retroviruses and Opportunistic Infections held each winter, the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) held each fall, the biannual International AIDS Conference, and various smaller gatherings—sometimes devoted to specific topics

like drug resistance or complications of therapy—organized by groups such as the International AIDS Society, the British HIV Association, and the European AIDS Clinical Society. In addition, pharmaceutical companies commonly sponsor meetings to present the latest research on their experimental drugs.

The most interesting or groundbreaking studies are usually presented orally by one of the authors, often accompanied by slides. While study abstracts are typically submitted months in advance, important last-minute results are sometimes included as “late-breakers.” Research that is not selected for oral sessions may be presented on posters. Abstracts from both oral and poster presentations are typically published in a catalog and may also be made available on the web.

### Medical Journals

The “gold standard” for the presentation of medical research is publication in a peer-reviewed professional journal. Journal editors send out submitted articles for review, usually by 1–4 selected colleagues who work in the same field, to ensure that the study appears well designed, the methods sound, and the data plausible.

There are several “tiers” of journals that publish medical research, from general science magazines like *Science* and *Nature*; to broad medical publications such as *The Lancet*, *Journal of the American Medical Association*, and *New England Journal of Medicine*; to specialized journals such as *AIDS*, *Clinical Infectious Diseases*, and *Journal of Virology*. Medical journal articles adhere to a basic standard format and usually include the following elements:

- **Abstract/Summary.** A short synopsis of a research article laying out the objective or goal of the study, the trial design and methods, a summary of the results obtained (and usually their statistical significance), and the authors’ conclusion or “take home” message.
- **Introduction/Background.** This usually includes a statement summarizing the problem or issue to be investigated, a brief review of what is known to date (with references to key literature), the rationale for the study (why was it done?), and the hypothesis (what did the authors hope to show?).
- **Design and Methods.** These sections (which may be combined) provide in-depth information about how the study was designed and carried out, including a detailed description of the study population, which treatment(s) were used, which tests were performed, and how data was collected and analyzed.
- **Results.** This section gives a detailed description of the data collected by the researchers and the results of their statistical analyses, often including tables, charts, and graphs.
- **Discussion.** In this section the authors interpret their results, draw their conclusions, and discuss what their findings mean—for example, whether the initial hypothesis was confirmed, how the results might affect clinical practice, potential limitations of the study, and suggestions for further research.

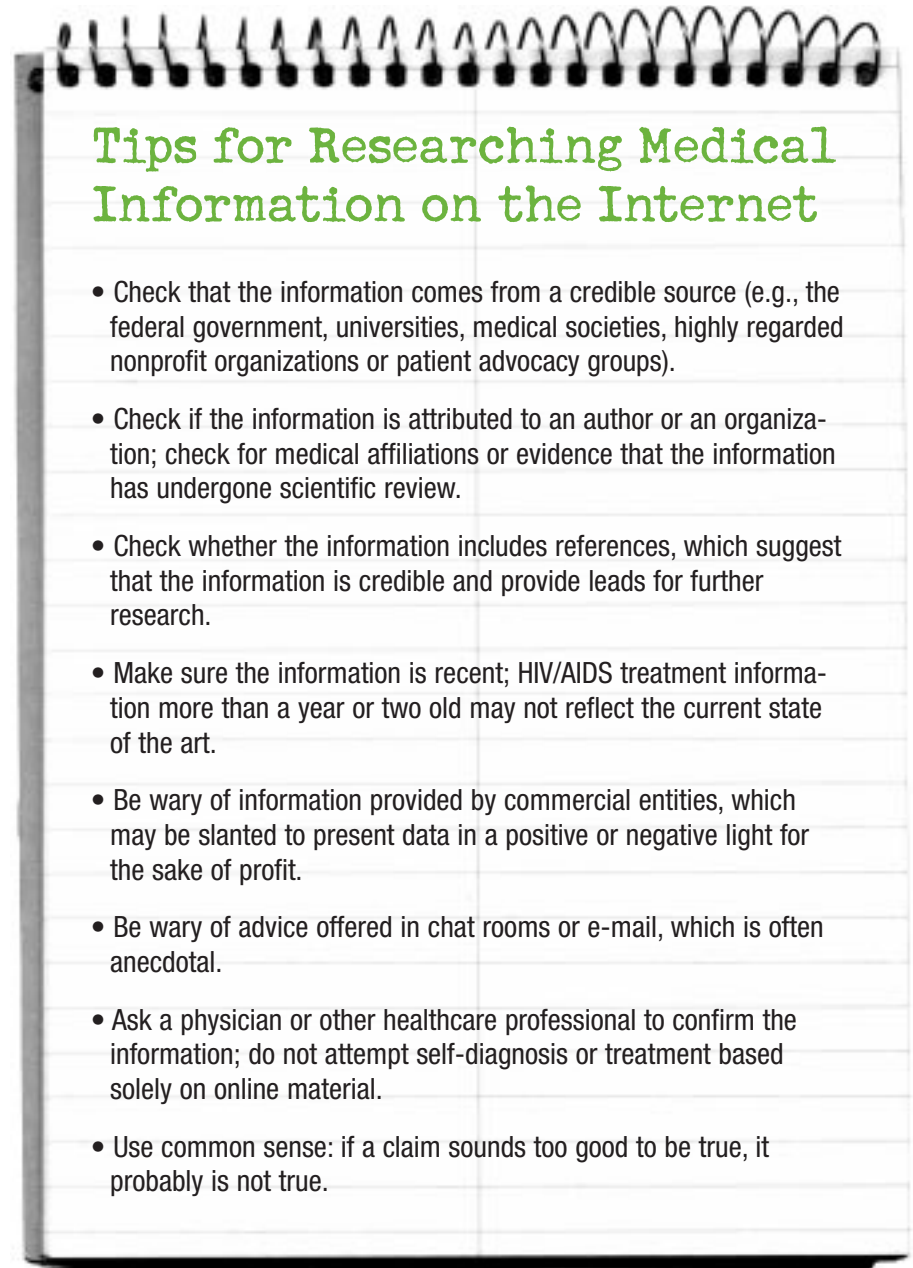
### Finding Useful Research Results

With improvements in information technology—and a shift away from the notion that medical professionals are unquestionable authorities—a growing number of people have taken an interest in exploring medical research for themselves. But just because a great deal of medical information is available on the Internet and elsewhere does not suggest that all of it is credible.

The most comprehensive source of peer-reviewed medical literature is MEDLINE, a database of more than 10 million references. MEDLINE can be accessed online using a variety of front-end tools including PubMed, a search service provided by the U.S. National Library of Medicine. With so much information available, entering a broad search term like “HIV” can feel like taking a drink from a fire hose. Users will obtain more useful and relevant results using narrower search criteria, for example a specific drug name or side effect.

MEDLINE provides free access to research abstracts, but users often must dig up actual medical journals to obtain the full text of articles. University and medical center libraries carry the most popular, reputable medical journals, and usually a selection of smaller, more specialized ones as well. Although intended for use by students and staff, some university libraries allow members of the public to access their collections. Most medical journals are available on the web, but generally offer only abstracts for free. Some provide immediate free full-text access to studies deemed particularly important or groundbreaking, and others offer full access to issues that are more than six months or a year old.

Other good online sources of medical information include sites sponsored by the federal government (e.g., National Institutes of Health, Centers for Disease Control and Prevention), universities (e.g., HIV InSite, Johns Hopkins AIDS Service), medical societies (e.g., International AIDS Society, American Society for Microbiology), nonprofit organizations (e.g., American Liver Foundation, American Heart Association), and patient advocacy and support groups (e.g., San Francisco AIDS Foundation, Project Inform, Hepatitis C Support Project). There are several independent sources of high-quality HIV/AIDS information supported by pharmaceutical companies, including AIDSmeds.com, The Body, and HIVandHepatitis.com.



## Tips for Researching Medical Information on the Internet

- Check that the information comes from a credible source (e.g., the federal government, universities, medical societies, highly regarded nonprofit organizations or patient advocacy groups).
- Check if the information is attributed to an author or an organization; check for medical affiliations or evidence that the information has undergone scientific review.
- Check whether the information includes references, which suggest that the information is credible and provide leads for further research.
- Make sure the information is recent; HIV/AIDS treatment information more than a year or two old may not reflect the current state of the art.
- Be wary of information provided by commercial entities, which may be slanted to present data in a positive or negative light for the sake of profit.
- Be wary of advice offered in chat rooms or e-mail, which is often anecdotal.
- Ask a physician or other healthcare professional to confirm the information; do not attempt self-diagnosis or treatment based solely on online material.
- Use common sense: if a claim sounds too good to be true, it probably is not true.

Pharmaceutical company web sites can provide useful information (in particular, full prescribing information for specific drugs) but beware of bias. To address concerns that unfavorable study data about experimental drugs have not been widely available, the industry trade group Pharmaceutical Research and Manufacturers of America (PhRMA) recently launched an online repository of published and unpublished clinical trial results at [www.clinicalstudyresults.org](http://www.clinicalstudyresults.org). (See the sidebar on this page for tips on

locating credible medical information on the Internet).

### Cautions to Keep in Mind

When reading medical literature, there are several potential pitfalls to keep in mind. Researchers understandably wish to produce interesting and groundbreaking results, and may have a conscious or unconscious tendency to make their findings appear more promising or more conclusive than they actually are. Likewise, journal editors want to publish studies

that attract readers and advance the state of the science.

These motivations contribute to a phenomenon known as **publication bias**, whereby studies are more likely to be published if they produce positive results (not necessarily “good” results, but those that confirm the investigators’ initial hypotheses). Studies that produce negative results—for example, that an investigational agent works no better than existing therapies—are less likely to see the light of day.

A potentially more serious concern is the desire of pharmaceutical companies to make their experimental therapies look as good as possible in the hopes of obtaining FDA approval and the large profits a successful anti-HIV drug could bring. This concern extends to researchers who have financial ties to the pharmaceutical industry or a personal financial stake in the outcome of a clinical trial (for example, owning stock in a drug company or holding a patent on an experimental agent).

### **Post-Hoc Manipulations**

Researchers may attempt to make their findings appear more positive by essentially changing the rules after the game has started (*post hoc* means “after the fact”). That is, they may fail to follow the procedures and methods set forth in their original protocol. Sometimes this is unavoidable; for example, it is not uncommon for researchers to broaden inclusion criteria, remove exclusion criteria, or settle for a smaller sample size because they have trouble recruiting enough suitable subjects.

One common way researchers may deviate from their original protocol is to analyze subjects based on the treatment they actually received rather than the one they were initially assigned. This is the difference between an **as-treated** and an **intent-to-treat** analysis. An intent-to-treat analysis uses data from all participants who were initially enrolled in a given study arm, whether or not they

stayed on the assigned treatment. An as-treated analysis excludes subjects who ended up not receiving the originally assigned intervention for the intended length of time, often because they withdrew from the study prematurely (for example, due to intolerable side effects) or because the treatment was not working. Using an as-treated analysis presents problems because subjects who do not receive their assigned treatment for the full, specified period tend to differ in systematic ways from those who remain on their assigned therapy the whole time (known as **exclusion** or **attrition** bias).

For example, say a study includes two arms, each with 100 subjects, randomly assigned to receive two different drug regimens for 48 weeks. In arm A, 90 subjects remain on their assigned regimen for the initially specified period and 60 of these achieve an undetectable HIV viral load (a response rate of about 66%). In arm B, 50 subjects remain on their assigned regimen for the whole time and 40 of these achieve an undetectable viral load (a response rate of 80%). But the other 50 participants drop out of the study early because they are unable to tolerate the side effects of the experimental drugs. In this case, it would not be fair to conclude that regimen B is superior to regimen A, because its usefulness is limited by a high rate of toxicity.

Researchers may also be tempted to exclude from their analysis subjects who fail to achieve good adherence. Perhaps regimen B appears more effective in those who actually take it as directed, but it is much less convenient (e.g., more pills per day or stricter food requirements), resulting in poor adherence.

To avoid this pitfall, researchers should account for all subjects who were initially assigned to a given study arm, whether or not they continued to receive the intended intervention for the entire period. At the very least, if the investigators analyze only those participants who successfully com-

pleted the initially specified course of therapy, they should clearly state that they performed an as-treated analysis. In practice, it is not uncommon for researchers to provide both intent-to-treat and as-treated results, especially if they differ considerably; typically, as-treated data make an intervention look more promising than the corresponding intent-to-treat results.

Another way researchers may attempt to find a silver lining in negative results is to perform various unplanned subgroup analyses. For instance, they may “mine” or “dredge” their data to see if anything promising turns up. This is a problem because in any study, some positive association for some subgroup of subjects is likely to occur by chance alone. A possible example of inappropriate subgroup analysis came to light in February 2003 when VaxGen announced that its AIDS VAX vaccine appeared to protect African-American subjects from contracting HIV, although this effect was not seen in the study population as a whole. Critics argued that the racial subgroup was too small (314 blacks out of 5,009 “high-risk” volunteers) and that the researchers failed to make appropriate adjustments in their analysis, thus overestimating the statistical significance of the results. To circumvent such concerns, investigators should specify at the outset what they are looking for, what types of analyses they plan to conduct, and how they will stratify their subjects.

Finally, it is not unknown for researchers to perform a variety of unusual and esoteric statistical tests in an attempt to turn up something worth reporting. If the authors of a study include statistical manipulations that are not the norm for the type of trial they conducted, they should clearly explain why.

### **Living in the Real World**

When exploring medical literature, it is important to bear in mind

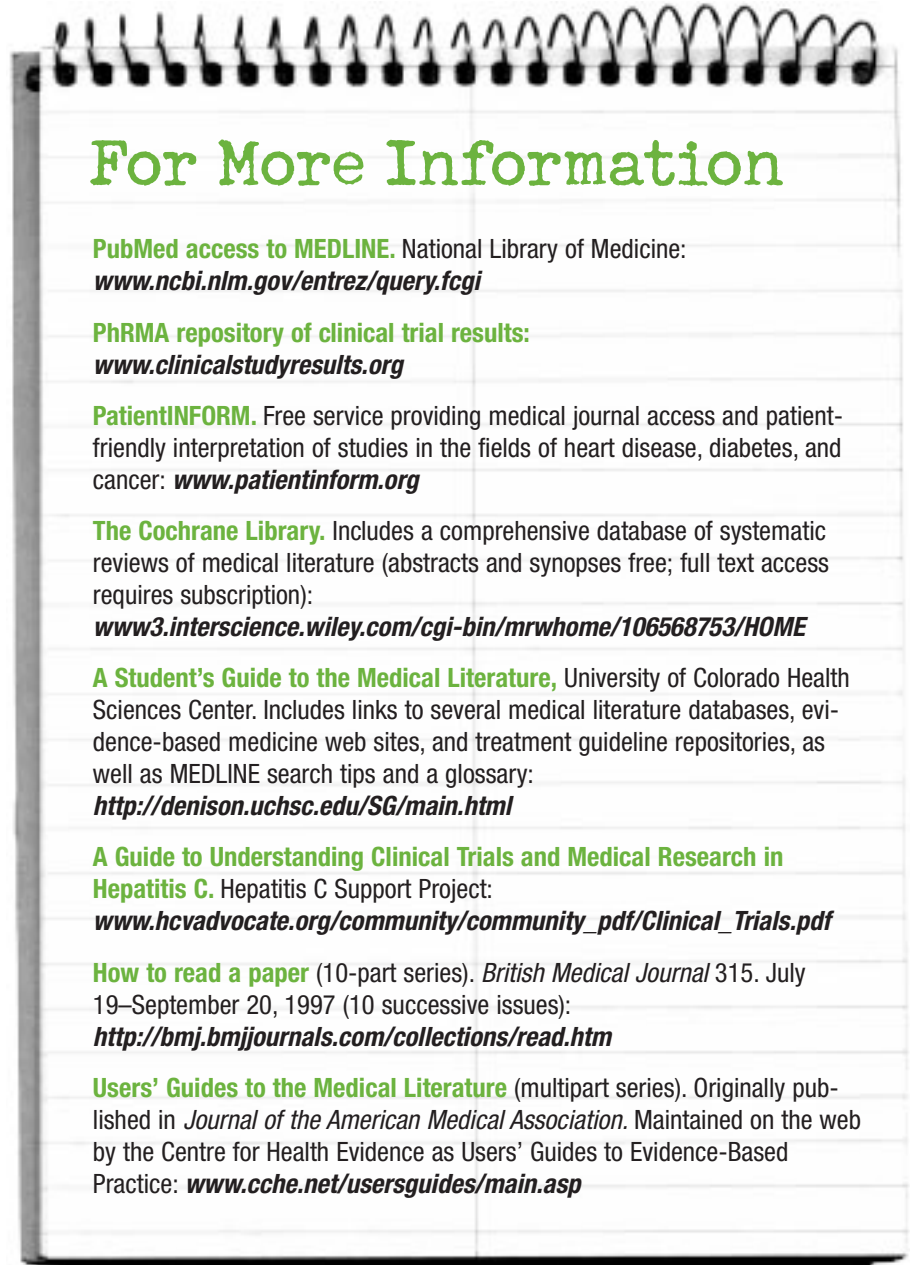
that statistical significance does not always imply clinical significance. A study might find, for example, that drug A increases subjects' CD4 cell counts by 5 cells/mm<sup>3</sup> while drug B increases CD4 counts by 10 cells/mm<sup>3</sup>. If the study was large enough, this difference might prove statistically significant, but it may still be essentially meaningless in terms of the actual clinical benefit it offers to people with HIV.

In addition, it is important to think about whether the results of a study can be **generalized** to other people with the disease. For example, if an HIV trial had strict exclusion criteria (not admitting individuals with HCV coinfection or a history of injection drug use or psychiatric conditions, say), or was unattractive to a certain subset of potential subjects (such as requiring frequent clinic visits to a remote location, such that low-income women with children found it impossible to participate), its outcome—no matter how promising—might be essentially irrelevant to a large proportion of the HIV positive population.

### Conclusion: Making the Most of Medical Research

Medical research is typically written for professionals, and can be difficult for nonspecialists to comprehend. However, with a basic grasp of clinical trial design and statistics, a good medical dictionary or glossary (available online), awareness of a few common pitfalls, and a bit of practice, most people should be able to understand the language of medical literature.

Recent events—including the soaring cost of prescription medications and controversy over the safety of certain classes of FDA-approved drugs—have focused unprecedented attention on medical research in the past year. The FDA has been accused of being too lax in demanding that drug companies conduct the required post-marketing studies to ensure that their products are safe over the long-term. The medical publishing field has been criticized for its propensity



## For More Information

**PubMed access to MEDLINE.** National Library of Medicine:  
[www.ncbi.nlm.gov/entrez/query.fcgi](http://www.ncbi.nlm.gov/entrez/query.fcgi)

**PhRMA repository of clinical trial results:**  
[www.clinicalstudyresults.org](http://www.clinicalstudyresults.org)

**PatientINFORM.** Free service providing medical journal access and patient-friendly interpretation of studies in the fields of heart disease, diabetes, and cancer: [www.patientinform.org](http://www.patientinform.org)

**The Cochrane Library.** Includes a comprehensive database of systematic reviews of medical literature (abstracts and synopses free; full text access requires subscription):  
[www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME](http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME)

**A Student's Guide to the Medical Literature,** University of Colorado Health Sciences Center. Includes links to several medical literature databases, evidence-based medicine web sites, and treatment guideline repositories, as well as MEDLINE search tips and a glossary:  
<http://denison.uchsc.edu/SG/main.html>

**A Guide to Understanding Clinical Trials and Medical Research in Hepatitis C.** Hepatitis C Support Project:  
[www.hcvadvocate.org/community/community\\_pdf/Clinical\\_Trials.pdf](http://www.hcvadvocate.org/community/community_pdf/Clinical_Trials.pdf)

**How to read a paper** (10-part series). *British Medical Journal* 315. July 19–September 20, 1997 (10 successive issues):  
<http://bmj.bmjournals.com/collections/read.htm>

**Users' Guides to the Medical Literature** (multipart series). Originally published in *Journal of the American Medical Association*. Maintained on the web by the Centre for Health Evidence as Users' Guides to Evidence-Based Practice: [www.cche.net/usersguides/main.asp](http://www.cche.net/usersguides/main.asp)

to publish mostly positive studies, and proposals have been put forth to make all clinical trial results available for free over the Internet. There has been increased scrutiny of conflicts of interest within the medical research and regulatory establishments, leading to stricter rules about consulting arrangements and stock ownership. Finally, concern has arisen about how the pharmaceutical industry shapes the overall research agenda by focusing on “lifestyle” and “me too” drugs that stand to produce large profits,

rather than therapies that will provide the most good for the most people.

As researchers, clinicians, regulators, and politicians sort out these difficult issues, people affected by HIV and other disease can protect themselves by arming themselves with knowledge.

*A Guide to Clinical Trials, Part I and II, were prepared for the San Francisco AIDS Foundation by Liz Highleyman.*

# Open Clinical Trials

**B**elow is a selected listing of currently enrolling clinical trials gathered from various sources. **TrialSearch**, operated by the **AIDS Community Research Initiative of America (ACRIA)**, is an extensive online database of clinical trials related to HIV/AIDS. The University of California at San Francisco's **HIV InSite** web site features **TrialScope**, a database of organizations that conduct HIV/AIDS-related research.

The federal government's **AIDSinfo** site includes a section on clinical trials that features an introduction to HIV/AIDS research and study listings from the National Institutes of Health's **ClinicalTrials.gov** database. **AIDSinfo** also offers personalized advice about clinical trial participation via e-mail (ContactUs@AIDSinfo.nih.gov), an interactive web site ([www.aidsinfo.nih.gov/live\\_help](http://www.aidsinfo.nih.gov/live_help); specialists available Mon.–Fri. 9:00 am–1:00 pm PT), and a toll-free telephone service (800-874-2572, international 301-874-2572; specialists available Mon.–Fri. 9:00 am–2:00 pm PT). **CenterWatch** is a commercial web site that includes trial listings for all diseases including HIV/AIDS and related conditions.

The majority of U.S. government-sponsored HIV/AIDS trials are conducted by the **AIDS Clinical Trials Group (ACTG)**, a nationwide network of investigators and medical centers. **The National Center for Complementary and Alternative Medicine (NCCAM)** conducts trials of complementary therapies for conditions related to HIV and its treatment. The **HIV Vaccine Trials Network (HVTN)** is an international collaboration testing preventive HIV vaccines.

**Community Programs for Clinical Research on AIDS (CPCRA)** is a nationwide network that conducts community-based clinical trials. In addition to **TrialSearch**, **ACRIA** also provides a listing of trials in the mid-Atlantic region. **The Community Research Initiative of New England (CRINE)** offers a listing of trials in the northeast.

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

**TrialSearch:** [www.acria.org/clinical\\_trials/index.html](http://www.acria.org/clinical_trials/index.html)

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

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

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

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

**ACTG:** [www.aactg.org](http://www.aactg.org)

**NCCAM:** [www.nccam.nih.gov/clinicaltrials/hiv.htm](http://www.nccam.nih.gov/clinicaltrials/hiv.htm)

**HIV Vaccine Trials Network:** [www.hvtn.org](http://www.hvtn.org)

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

**ACRIA:** [www.acria.org](http://www.acria.org)

**CRINE:** [www.crine.org/info/clinical.html](http://www.crine.org/info/clinical.html)

## Simplified Kaletra Regimen

Researchers have recently reported data from a study of Kaletra (lopinavir/ritonavir combination pill) used as monotherapy (see “Drug Watch” on page 15). This new, open-label Phase III study, sponsored by Abbott Laboratories, will look at another type of simplified Kaletra regimen. Treatment-naïve subjects will be randomly assigned to receive either a standard Kaletra-based regimen containing two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) or Kaletra plus a single NRTI, tenofovir DF (Viread).

Eligible subjects must be at least 18 years of age and must not have previously taken antiretroviral therapy. They must have a detectable HIV viral load (at least 400 copies/mL), but may have any CD4 cell count.

For locations and further information, call Abbott at 800-633-9110. [www.clinicaltrials.gov/ct/show/NCT00234910](http://www.clinicaltrials.gov/ct/show/NCT00234910) (ITAL-04-002).

An international Phase II study of Kaletra monotherapy sponsored by the Huesped Foundation is also currently enrolling in Vancouver, Mexico City, and Buenos Aires. One hundred subjects currently taking regimens consisting of Kaletra or another ritonavir-boosted protease inhibitor (PI) plus two NRTIs will have their regimen simplified to Kaletra alone. For more information, see [www.clinicaltrials.gov/ct/show/NCT00159224](http://www.clinicaltrials.gov/ct/show/NCT00159224) (ACA-ARGE-04-001).

## TMC114: Treatment-Naïve and Expanded Access

Researchers at the 2005 International AIDS Society meeting and the Interscience Conference on Antiretroviral Agents and Chemotherapy presented further promising data on TMC114, Tibotec's investigational PI, in treatment-experienced individuals (see “News Briefs” on page 10).

A new Phase III study, sponsored by Tibotec Pharmaceuticals, will compare the efficacy, safety, and tolerability of ritonavir-boosted TMC114 versus Kaletra in people starting anti-HIV therapy for the first time. Subjects will be randomly assigned to receive either TMC114/ritonavir or Kaletra, both with Truvada (emtricitabine/tenofovir combination pill), for 96 weeks. Eligible subjects must be at least 18 years of age, have viral loads of at least 5,000 copies/mL, and be starting antiretroviral therapy for the first time. Subjects may not have active opportunistic illnesses (OIs) or certain laboratory abnormalities. Women may not be pregnant or breast-feeding and participants must agree to use effective contraception. This trial aims to enroll 660 participants at some 25 U.S. sites, including **Austin, Baltimore, Ft. Lauderdale, Houston, Los Angeles, Miami, Orlando, Philadelphia, Phoenix, San Francisco, San Juan, Tampa, Winston-Salem, and Washington, DC**. For all sites, send e-mail to [info@veritasmedicine.com](mailto:info@veritasmedicine.com). [www.clinicaltrials.gov/ct/gui/show/NCT00258557](http://www.clinicaltrials.gov/ct/gui/show/NCT00258557) (TMC114-C211; CR002800).

In addition to this trial, in October 2005 Tibotec announced the launch of a TMC114 expanded access program (EAP) for people with limited treatment options. The program will provide free access to TMC114 for people with AIDS who need the drug to construct a viable treatment regimen (i.e., have experience with three antiretroviral drug classes, have used at least two PI-based regimens, and have a CD4 cell count of 200 cells/mm<sup>3</sup> or less) and who are not eligible for currently enrolling clinical trials. For more about the program, healthcare professionals and people with HIV/AIDS may call 866-889-2074 or send e-mail to [TMC114-C226@i3research.com](mailto:TMC114-C226@i3research.com). [www.clinicaltrials.gov/ct/show/NCT00245739](http://www.clinicaltrials.gov/ct/show/NCT00245739) (TMC114-C226; CR006304).

### TMC125: New NNRTI

Tibotec has also taken the unusual step of conducting clinical trials using two experimental agents, TMC114 and the company's investigational non-nucleoside reverse transcriptase inhibitor (NNRTI) TMC125 (see "News Briefs" on page 10). Two very similar Phase III trials, TMC125-C206 and TMC125-C216 (DUET 1 and 2), will look at the long-term safety, efficacy, and tolerability of regimens containing TMC125. In each study, 600 treatment-experienced HIV positive subjects with limited or no available treatment options will be randomly assigned to receive TMC125 or placebo; all participants will also receive ritonavir-boosted TMC114 plus an optimized background regimen. Eligible subjects must be at least 18 years of age and have HIV viral load greater than 5,000 copies/mL. They must have at least three primary PI resistance mutations as well as resistance to currently available NNRTIs. Exclusion

criteria include active OIs, certain abnormal laboratory results, and use of certain medications.

TMC125-206 is enrolling in **Little Rock, AK; Macon, GA; Santa Fe, NM; Huntersville, NC; Longview, TX; and Washington DC**. TMC125-216 is enrolling in **Palm Springs, Phoenix, and Washington, DC**. For both studies, send e-mail to [info@veritasmedicine.com](mailto:info@veritasmedicine.com). [www.clinicaltrials.gov/ct/show/NCT00254046](http://www.clinicaltrials.gov/ct/show/NCT00254046) (CR002752; TMC125-206); [www.clinicaltrials.gov/ct/show/NCT00255099](http://www.clinicaltrials.gov/ct/show/NCT00255099) (CR006307; TMC125-216).

### Maraviroc Studies Enrolling

Pfizer is conducting three currently enrolling trials looking at the safety and efficacy of its investigational HIV entry inhibitor maraviroc (UK-427,857), the subject of favorable reports at recent conferences (see "News Briefs" on page 9).

The first Phase II/III study will compare maraviroc against efavirenz (Sustiva) in individuals starting anti-HIV therapy for the first time. Subjects will be randomly assigned to receive 300 mg maraviroc once daily, 300 mg maraviroc twice daily, or efavirenz; all participants will also take AZT (zidovudine, Retrovir) and 3TC (lamivudine, Epivir). Participants will have regular clinic visits, some of which will include physical examinations, blood draws, electrocardiogram (EKG) heart rhythm monitoring, computerized tomography (CT) scans, and symptom questionnaires.

Eligible subjects must be at least 16 years of age and have viral load of at least 2,000 copies/mL. Subjects must have HIV that uses the CCR5 (rather than the CXCR4) coreceptor. Exclusion criteria include various medical conditions or abnormal laboratory results, current or prior use of certain medications, and resistance to study drugs. Women may not be pregnant or breast-feeding and participants must agree to use effective contraception.

This study will enroll more than 1,000 subjects at some 200 centers worldwide, including **Atlanta, Birmingham, Boston, Chicago, Cincinnati, Dallas, Denver, Houston, Indianapolis, Los Angeles, Miami, New York City, Oakland, Omaha, Philadelphia, Sacramento, San Francisco, San Juan, Tacoma, and Tampa**. For all sites, call Pfizer at 800-718-1021. [www.clinicaltrials.gov/ct/show/NCT00098293](http://www.clinicaltrials.gov/ct/show/NCT00098293) (A4001026).

The other two Phase II/III trials will look at the safety and efficacy of maraviroc plus optimized background therapy (OBT). Treatment-experienced individuals will be randomly assigned to receive 150 mg maraviroc once daily, 150 mg maraviroc twice daily, or placebo; all participants will also take OBT determined on the basis of treatment history and resistance testing. Participants will receive

regular clinic visits, some of which will include physical examinations, blood draws, and EKGs.

Eligible subjects must be at least 16 years of age and have viral load of at least 5,000 copies/mL. They must have been on stable HAART, or else no antiretroviral therapy, for at least four weeks. Subjects must have at least six months experience with, or documented resistance to, three of the four classes of approved anti-HIV drugs. Exclusion criteria include various medical conditions or abnormal laboratory results and current or prior use of certain medications. Women may not be pregnant or breast-feeding and participants must agree to use effective contraception.

These studies aim to enroll 500 participants at nearly 100 sites in the U.S., including **Albany, Albuquerque, Atlanta, Baltimore, Baton Rouge, Birmingham, Boston, Cincinnati, Dallas, Denver, Durham, Houston, Los Angeles, Madison, Miami, Minneapolis, New Orleans, New York City, Oakland, Omaha, Orlando, Philadelphia, Phoenix, Rochester, Sacramento, San Francisco, San Juan, St. Louis, Tacoma, Tampa, Wichita, and Washington, DC**, as well as several international locations. For all sites, call Pfizer at 800-718-1021.

[www.clinicaltrials.gov/ct/show/NCT00098306](http://www.clinicaltrials.gov/ct/show/NCT00098306) (A4001027);  
[www.clinicaltrials.gov/ct/show/NCT00098722](http://www.clinicaltrials.gov/ct/show/NCT00098722) (A4001028).

### ***New Oral Entry Inhibitor: SP01A***

Based on promising Phase I/II results, Samaritan Pharmaceuticals is now enrolling a Phase II monotherapy trial to assess the safety, efficacy, and optimal dosing of its experimental oral entry inhibitor, SP01A, in treatment-experienced individuals. After a 40-day washout period of all current anti-HIV drugs, participants will be randomly assigned to receive one of three doses of SP01A or placebo for 10 days; a 28-day monotherapy study is also underway.

Eligible subjects must be 18–60 years of age and experiencing virological failure despite antiretroviral therapy; CD4 cell count must be at least 50 cells/mm<sup>3</sup>. Patients currently on stable antiretroviral regimens that are successfully suppressing HIV (below 5,000 copies/mL) are not eligible. Exclusion criteria include various medical conditions (including active OIs or hepatitis) or abnormal laboratory results and use of certain medications (including sulfonamide drugs). Women may not be pregnant or breast-feeding and must agree to use effective contraception.

This study aims to enroll 92 subjects at six sites including **Fort Lauderdale** (954-564-4222), **Fort Worth** (817-810-9810), **Miami** (305-792-2090), **Orlando** (407-647-3960 ext. 2118), **Pittsburgh** (412-661-17163), and **Tampa** (813-875-4374).

[www.clinicaltrials.gov/ct/show/NCT00113412](http://www.clinicaltrials.gov/ct/show/NCT00113412) (SP01A-105-04).

### ***Fixed Dose Combination Pills***

This randomized Phase IV postmarketing study, sponsored by GlaxoSmithKline, will compare the long-term safety and efficacy of two double-NRTI fixed-dose combination pills—Glaxo’s Epzicom (abacavir/3TC) and Gilead Sciences’ Truvada (emtricitabine/tenofovir)—used in combination with Kaletra for 96 weeks.

Eligible subjects must be at least 18 years of age, have viral loads of at least 1,000 copies/mL, and be starting antiretroviral therapy for the first time. Subjects may not have active OIs, pancreas or kidney dysfunction, or active hepatitis, and may not be taking medications that may interfere with the study drugs. Women may not be pregnant, breast-feeding, or planning to become pregnant during the two-year study period, and must use effective contraception.

This study will enroll 680 subjects at nearly 100 sites including **Atlanta, Austin, Baltimore, Charlotte, Chicago, Denver, Detroit, Houston, Las Vegas, Los Angeles, Louisville, Miami, Milwaukee, Newark, New Orleans, New York City, Oakland, Orlando, Philadelphia, Rochester, San Francisco, San Juan, St. Louis, Tampa, Toledo, Tucson, Tulsa, and Washington, DC**. For all sites, call Glaxo at 877-379-3718.

[www.clinicaltrials.gov/ct/show/NCT00244712](http://www.clinicaltrials.gov/ct/show/NCT00244712) (EPZ104057).

### ***SLAM-C: Pegylated Interferon Maintenance Therapy for HIV/HCV Coinfection***

Past research has shown that liver damage due to hepatitis C progresses more rapidly in HIV positive people. Coinfected people do not respond as well to hepatitis C treatment as individuals with hepatitis C virus (HCV) alone, but some studies suggest that long-term interferon maintenance therapy may help slow liver disease progression even in the absence of a sustained virological response.

In this open-label Phase II study, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), subjects who either have never received therapy for hepatitis C or who did not clear HCV with prior treatment will receive a standard course of HCV therapy (180 mcg Pegasys brand pegylated interferon-alfa-2a once weekly plus weight-based ribavirin daily). Subjects who respond well after 12 weeks will continue on this regimen for an additional 60 weeks. Those who respond poorly will be randomly assigned either to stop ribavirin and continue pegylated interferon for 72 weeks, or to discontinue both ribavirin and pegylated interferon. Follow-up will continue for 90–96 weeks. Participants will receive liver biopsies at study entry, after changing therapy, and at the end of follow-up to monitor progression of fibrosis (liver scarring).

Eligible participants must be at least 18 years of age and have chronic hepatitis C with elevated liver enzyme (ALT, AST, and alkaline phosphatase) levels and at least stage I fibrosis. They must have been on stable anti-HIV therapy for at least eight weeks or else off antiretroviral therapy for four weeks. They must have HIV viral load below 50,000 copies/mL and CD4 cell counts of at least 200 cells/mm<sup>3</sup>. They must either be naive to hepatitis C therapy or else still have detectable HCV RNA after previous treatment with standard or pegylated interferon with or without ribavirin. Exclusion criteria include various medical conditions (including decompensated liver cirrhosis, hepatitis B, autoimmune diseases, and uncontrolled depression or other psychiatric conditions) and current or prior use of certain medications. Women may not be pregnant or breast-feeding and participants must agree to use effective contraception.

This study aims to enroll 180 subjects at more than 40 sites, including **Atlanta** (404-616-6313), **Baltimore** (410-614-2766), **Birmingham** (205-975-7925), **Boston** (617-724-0072), **Buffalo** (716-898-3933), **Chapel Hill** (919-843-8761), **Chicago** (312-695-5012), **Cincinnati** (513-584-8373), **Cleveland** (216-778-5489), **Dallas** (214-590-0414), **Denver** (303-372-5535), **Galveston** (409-747-0241), **Honolulu** (808-737-2751), **Indianapolis** (317-630-6023), **Los Angeles** (310-825-1301), **Miami** (305-243-3838), **Nashville** (615-467-0154 ext. 108), **New York City** (212-746-7198), **Omaha** (402-559-8163), **Philadelphia** (215-349-8092), **Pittsburgh** (412-647-0771), **Providence** (401-793-4396), **Rochester** (585-275-2740), **San Francisco** (415-514-0550 ext. 354), **San Juan** (787-759-9595), **St. Louis** (314-454-0058), and **Washington, DC** (202-687-7387).  
[www.clinicaltrials.gov/ct/show/NCT00078403](http://www.clinicaltrials.gov/ct/show/NCT00078403)  
(ACTG A5178; SLAM-C).

### ***Nucleoside Supplement for Lipoatrophy***

This open-label Phase II study, sponsored by NIAID, will assess whether use of a nucleoside-rich nutritional supplement or switching from the thymidine analog NRTIs AZT or d4T (stavudine, Zerit) to tenofovir can help reverse peripheral fat loss (lipoatrophy) believed to be associated with mitochondrial toxicity in people with HIV. The supplement, NucleomaxX, is a sugar cane extract containing the nucleoside uridine, a building block of genetic material. The researchers hypothesize that nucleoside supplementation may help counteract the adverse effects of NRTIs by increasing mitochondrial DNA in fat tissue; preliminary data suggest that NucleomaxX can help alleviate lipoatrophy related to AZT or d4T (see “Nutrition and HIV” on page 27). Participants will be randomly assigned to receive NucleomaxX every other day for 48 weeks, or to switch from AZT or d4T to tenofovir.

Subjects will have 10 study visits, which will include blood draws and other tests.

Eligible participants must be at least 18 years of age with HIV viral load below 50 copies/mL and diagnosed HIV-related lipoatrophy. They must be on stable antiretroviral regimens that include AZT or d4T. Exclusion criteria include certain medical conditions (including diabetes requiring medication) and abnormal laboratory tests. Women may not be pregnant or breastfeeding.

This study will enroll 50 subjects at the University Hospitals of **Cleveland** (216-844-2460).  
[www.clinicaltrials.gov/ct/show/NCT00119379](http://www.clinicaltrials.gov/ct/show/NCT00119379)  
(1R01-AI060484-01A2B).

### ***L-Carnitine for Fatigue***

This Phase II study, sponsored by the National Institute of Nursing Research, will examine whether supplementation with the micronutrient levocarnitine (L-carnitine), which plays a role in energy metabolism, can help alleviate fatigue and related symptoms in carnitine-deficient subjects with AIDS. Participants will be randomly assigned to receive either L-carnitine or placebo; after two weeks, all participants who initially received the placebo will be switched over to L-carnitine, and everyone will continue on L-carnitine for two more weeks.

Eligible participants must be at least 18 years of age with diagnosed AIDS (stage IV-C) and persistent clinically significant fatigue. Subjects may not have certain medical conditions, including history of seizure disorders, dementia, or cognitive impairment.

This study aims to enroll 44 participants at Beth Israel Medical Center in **New York City** (212-420-4748).  
[www.clinicaltrials.gov/ct/show/NCT00079599](http://www.clinicaltrials.gov/ct/show/NCT00079599)  
(1 R21 NR08295-01).

### ***Nutritional Supplement for Insulin Resistance***

This Phase II/III study, sponsored by the National Center for Complementary and Alternative Medicine, will assess whether use of the nutritional supplement chromium picolinate can help reduce insulin resistance or glucose intolerance—a precursor to diabetes—in people with HIV. Previous research suggests that chromium picolinate helps improve insulin sensitivity in HIV negative individuals with type 2 diabetes mellitus. Participants will be randomly assigned to receive either chromium picolinate or placebo once daily for two months. There will be four overnight visits plus two additional daytime visits.

Eligible participants must be at least 18 years of age and currently taking combination antiretroviral therapy. They must have HIV viral load below 35,000 copies/mL and CD4 cell counts of at least 300 cells/mm<sup>3</sup>. Exclusion criteria include certain medical conditions (including

diabetes requiring medication) and abnormal laboratory tests. Women may not be pregnant.

This study will enroll 40 participants at the State University of New York General Clinical Research Center in **Stony Brook** (631-444-1175).

[www.clinicaltrials.gov/ct/show/NCT00109746](http://www.clinicaltrials.gov/ct/show/NCT00109746) (AT002499-01A1).

### **Protease Inhibitors and Glucose Metabolism**

This randomized Phase IV study, sponsored by the Department of Veterans Affairs, will attempt to determine how PIs contribute to the development of diabetes in people with HIV—in particular, whether PIs impair insulin secretion and increase the production of glucose by the liver. In order to separate out the effects of PIs from those of HIV itself, this study will use HIV negative volunteers. Participants will be randomly assigned to receive either a single dose of a PI or placebo. Somatostatin and growth hormone will be administered to control insulin and glucagon production. Insulin secretion will be assessed using the hyperglycemic clamp technique. Liver glucose production will be measured in the fasting and hyperinsulinemic (excess insulin) states.

This study aims to enroll 80 healthy, HIV negative participants between 18 and 72 years of age. Volunteers may not have medical conditions associated with insulin resistance, such as obesity or elevated blood fat levels, and may not be taking glucocorticoids, growth hormone, niacin, or antipsychotic medications. Women may not be pregnant. This study will take place at the **San Francisco** Veterans Affairs Medical Center (415-221-4810 ext. 2118).

[www.clinicaltrials.gov/ct/show/NCT00259727](http://www.clinicaltrials.gov/ct/show/NCT00259727) (RCD-005-05S; H574-23263).

### **Kaletra for HIV Positive Infants**

This nonrandomized, open-label Phase I study, sponsored by NIAID and the National Institute of Child Health and Human Development (NICHD), will assess the safety and tolerability of the PI Kaletra in HIV positive infants up to six months old; the drug is currently approved for adults and children over six months of age. The study also aims to determine the most effective Kaletra dose for infants, and whether early anti-HIV therapy promotes normal immune system development. Infants will receive Kaletra plus two NRTIs chosen by their physicians. They will have study visits every two weeks for the first eight weeks, then every four weeks until the end of the first year, then every 12 weeks; some visits will include pharmacokinetic monitoring. Infants will be followed for two years after the enrollment of the last participant.

Eligible infants must be between 14 days and six months of age and weigh more than 5.5 pounds (2.5

kilograms). They must have diagnosed HIV infection, with HIV viral load greater than 10,000 copies/mL within 30 days prior to study entry. Exclusion criteria include certain medical conditions (including active OIs), abnormal laboratory tests, and use of certain medications (including NNRTIs and other PIs).

This study will enroll 26 infants at more than 20 U.S. sites, including **Baltimore** (410-955-9749), **Boston** (617-355-8198), **Chapel Hill** (919-966-9110), **Chicago** (773-880-3669), **Denver** (303-861-6751), **Durham** (919-416-3447), **Jacksonville** (904-244-5331), **Memphis** (901-495-3490), **Miami** (305-243-4447), **Newark** (973-972-3118), **New Orleans** (504-586-3804), **New York City** (212-263-5680), **Oakland** (510-428-3885 ext. 2827), **San Diego** (619-543-8080), **San Francisco** (415-476-6480), **San Juan** (787-765-4186), and **Washington, DC** (202-865-4578). [www.clinicaltrials.gov/ct/show/NCT00038480](http://www.clinicaltrials.gov/ct/show/NCT00038480) (PACTG P1030).

### **Kaletra Interaction with the Contraceptive Patch**

Past research has shown that several PI and NNRTI drugs interact with oral contraceptives; however, this may be less of a concern with a transdermal contraceptive patch that bypasses the common metabolic pathway. This nonrandomized Phase II study, sponsored by NIAID, will assess interactions between Kaletra (lopinavir/ritonavir) and hormonal oral and transdermal contraceptives. Women will receive a single dose of the Ortho Novum 1/35 contraceptive pill on the first day of the study and will start the Ortho Evra contraceptive patch on the third day. Blood levels of lopinavir and the hormone ethinyl estradiol will be measured throughout the six-week trial; liver enzyme levels and hormonal side effects will also be assessed.

Eligible women must be at least 13 years of age and weigh no more than 198 pounds (90 kilograms); women over age 35 must be nonsmokers. Women may be either HIV positive or HIV negative, with HIV viral load below 55,000 copies/mL and CD4 cell counts of at least 200 cells/mm<sup>3</sup>. They may be on a regimen containing Kaletra for at least 60 days prior to study entry, or on a NRTI-only regimen, or not taking any antiretroviral therapy for at least 30 days. Exclusion criteria include certain medical conditions (including cardiovascular or liver disease) and recent use of certain medications (including systemic hormonal therapies or glucocorticoids, NNRTIs, or tenofovir). Participants may not be pregnant, and will receive a pregnancy test at study entry.

This study aims to enroll 54 women at eight sites including **Baltimore** (410-706-1476), **Chicago** (773-257-5717), **Denver** (303-372-5535), **Honolulu** (808-737-2751), **Los Angeles** (323-226-2226), **New Haven** (203-688-6093), and **Seattle** (206-731-8877). [www.clinicaltrials.gov/ct/show/NCT00125983](http://www.clinicaltrials.gov/ct/show/NCT00125983) (AACTG A5188).

### Tenofovir to Prevent Perinatal HIV Transmission

Recent data showing that single-dose nevirapine for prevention of mother-to-child transmission (MTCT) can lead to rapid resistance have spurred the search for other convenient and inexpensive perinatal prevention strategies.

This Phase I trial, sponsored by NIAID and NICHD, will look at the safety, tolerability, and pharmacokinetics of single-dose tenofovir given to women during labor and to their newborn infants. Tenofovir has been shown to effectively reduce MTCT in monkeys infected with a simian virus related to HIV. In this nonrandomized, open-label study, pregnant women will be assigned to one of two groups. Subjects in Cohort 1 will receive a single 600 mg dose of tenofovir at the start of labor or before planned cesarean section. They will also receive intravenous AZT (standard therapy for preventing MTCT in developed countries) and/or other antiretroviral medications prescribed by their physicians. Infants born to women in Cohort 1 will receive the standard six-week postpartum AZT prophylaxis regimen. After eight-week data from infants in Cohort 1 have been analyzed, a second cohort of pregnant women will receive single-dose tenofovir (with the dose to be determined based on pharmacokinetic data from Cohort 1) plus standard AZT prophylaxis and/or other antiretroviral drugs. Infants born to women in Cohort 2 will receive a single dose of tenofovir six hours after birth along with the standard AZT regimen. Several blood samples will be collected from mothers and infants. The women will be followed for 12 weeks postpartum; if viral resistance to tenofovir emerges during this period, they will be followed for two years. The infants will be followed until age 2.

Eligible women must be at least 18 years of age and in their third trimester of pregnancy (at least 34 weeks gestation). There are no viral load or CD4 cell count restrictions. Exclusion criteria include various medical conditions, abnormal laboratory results, and current or prior use of certain medications. Ultrasound screening must show a normal pregnancy and mothers must agree not to breast-feed.

This study aims to enroll 20 women at more than 20 sites including **Boston** (617-355-8198), **the Bronx** (718-960-1020), **Chicago** (773-257-5717), **Denver** (303-861-6751), **Detroit** (313-745-7857), **Durham** (919-416-3447), **Houston** (832-824-1339), **Los Angeles** (323-226-2226), **Memphis** (323-669-2390), **Miami** (305-243-4447), **Newark** (973-972-3118), **New York City** (212-263-5680), **Philadelphia** (215-427-5284), **San Diego** (619-543-8080), and **San Juan** (787-765-4186).  
[www.clinicaltrials.gov/ct/show/NCT00076791](http://www.clinicaltrials.gov/ct/show/NCT00076791) (PACTG 394).

### Treatment During Early Infection

While some experts believe antiretroviral therapy should be started soon after HIV infection, it is not yet clear whether treatment of recently infected individuals leads to long-term benefit or harm. In this open-label study, sponsored by NIAID, participants newly infected with HIV will be randomly assigned to receive either no treatment or a regimen of Truvada (emtricitabine/tenofovir combination pill) plus Kaletra for 36 weeks; after 36 weeks, subjects in both arms will have the option to continue or start treatment if they have high viral load, low CD4 count, or HIV-related symptoms. HIV viral load will be measured at the end of treatment and at 72 and 96 weeks to determine whether early therapy appears to lower the viral “set point”; CD4 cell count, occurrence of AIDS-defining illnesses, adverse side effects, and drug resistance will also be assessed. Study visits will occur every 2–4 weeks for the duration of the 96-week trial.

Eligible subjects must be at least 18 years of age. They must be recently infected with HIV, with viral load of at least 500 copies/mL and CD4 cell counts of at least 350 cells/mm<sup>3</sup> within 21 days prior to study entry. Exclusion criteria include various medical conditions and use of certain medications (including prior antiretroviral therapy or investigational HIV vaccines). Women may not be pregnant or breast-feeding.

This study aims to enroll 150 participants at more than 30 sites including **Atlanta** (404-616-6313), **Boston** (617-724-0070), **Chapel Hill** (919-843-8761), **Denver** (303-372-5535), **Detroit** (313-916-2570), **Durham** (919-684-8216), **Indianapolis** (317-274-8456), **New York City** (212-327-7281), **Philadelphia** (215-349-8092), **Providence** (401-793-4396), **Rochester** (585-275-2740), **San Diego** (619-543-8080), **San Francisco** (415-476-9296 ext. 318), **Seattle** (206-731-8877), and **St. Louis** (314-454-0058).  
[www.clinicaltrials.gov/ct/show/NCT00090779](http://www.clinicaltrials.gov/ct/show/NCT00090779) (ACTG A5217; AIEDRP AIN503).

Subjects in this trial will also be encouraged to join AIEDRP CORE01, a long-term follow-up study of HIV positive individuals identified during early infection.  
[www.clinicaltrials.gov/ct/show/NCT00086372](http://www.clinicaltrials.gov/ct/show/NCT00086372).

### Project T: Tenofovir to Prevent HIV Infection

This study, conducted by the Centers for Disease Control and Prevention (CDC) in conjunction with the San Francisco Department of Public Health (SFDPH), will attempt to determine whether tenofovir can help prevent HIV infection. The drug has performed well in animal prevention studies and it has fewer side effects than most other antiretroviral medications. Participants will receive

either daily oral tenofovir or placebo. This phase of the study will focus on the clinical and behavioral safety of the drug rather than its effectiveness. In particular, researchers will attempt to determine whether using a potentially preventive drug will lead to an increase in risky sexual behavior. Because it is not yet known whether tenofovir can help prevent HIV infection—and because some subjects will receive placebo—participants should continue to practice safer sex, and will receive risk-reduction counseling and free condoms. Should any participants become infected, SFDPH will facilitate referrals for HIV care and treatment.

Eligible participants must be sexually active HIV negative men who have sex with men. The study is expected to last two years. The U.S. arm of the study will enroll 400 gay and bisexual men in **San Francisco** (415-554-9068; [www.sfaidresearch.org](http://www.sfaidresearch.org)) and **Atlanta**. The CDC is conducting similar studies in **Botswana** and **Thailand** looking at heterosexual and injection drug-using populations.

**ACE: Herpes Suppression to Prevent HIV Infection**

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

Eligible participants must be sexually active HIV negative gay or bisexual men at least 18 years of age with confirmed HSV-2 infection. The study will enroll some 300 participants in **San Francisco** (415-437-4782; [www.sfaidresearch.org](http://www.sfaidresearch.org)). There are other study sites for men who have sex with men in **Seattle** (206-520-3800 or 800-464-9063), **New York City** (212-388-0008; [www.projectachieve.org](http://www.projectachieve.org)), and **Lima, Peru**. A similar study of heterosexual women is being conducted in **Zimbabwe, Zambia, and South Africa**. [www.hptn.org/research\\_studies/hptn039.asp](http://www.hptn.org/research_studies/hptn039.asp) (HTPN 309).

**Reinfection with New HIV Strains**

Some research suggests that reinfection (or super-infection) with new strains of HIV may lead to faster disease progression (see “Dual Infection” on page 36). The

Positive Partners study will investigate the incidence of reinfection with genetically distinct viral strains—in particular drug-resistant strains—in HIV positive couples. Participants will have two confidential, one-on-one interviews over the course of one year, during which they will provide blood and (if male) semen samples. If viral load increases by 1 log, an additional visit may be necessary. Drug resistance tests will be conducted at least twice during the year and results will be provided to participants. Subjects will be reimbursed \$35 for each visit.

Eligible participants must be at least 18 years of age, taking antiretroviral therapy, and have a sexual partner who is also HIV positive and taking anti-HIV treatment. There are no CD4 cell count or viral load restrictions. The study will take place in **San Francisco**. For more information, call 415-734-4878 or send e-mail to [positivepartners@gladstone.ucsf.edu](mailto:positivepartners@gladstone.ucsf.edu). [www.gladstone.ucsf.edu/gladstone/site/pospart](http://www.gladstone.ucsf.edu/gladstone/site/pospart).

**Buprenorphine and HIV Primary Care**

This Phase IV study, sponsored by the University of California at San Francisco (UCSF), the New York Academy of Medicine, and the federal Health Resources and Services Administration, will assess the feasibility, effectiveness, and cost of integrating buprenorphine treatment for opiate dependence in an HIV primary care setting. Opiate-using subjects will receive HIV primary care from UCSF’s Positive Health Program at San Francisco General Hospital. They will be randomly assigned to receive 12 months of opiate-replacement therapy with buprenorphine either as part of their primary care or at a separate substance abuse treatment clinic. The study will look at the program’s effects on participant’s substance use and overall health.

Eligible subjects must be at least 19 years of age, meet the DSM-IVR criteria for opioid dependence, and plan to remain in San Francisco for 12 months. Exclusion criteria include coexisting alcohol or benzodiazepine dependence, liver dysfunction, certain types of psychiatric impairment, and certain other medical conditions. Women may not be pregnant or trying to become pregnant.

For more information, call 415-476-9296 ext. 311 or send e-mail to [rthawley@php.ucsf.edu](mailto:rthawley@php.ucsf.edu). [www.clinicaltrials.gov/ct/show/NCT00263458](http://www.clinicaltrials.gov/ct/show/NCT00263458) (H97HA03799).

## APPROVED ANTIRETROVIRAL DRUGS

GENERIC (COMMON) NAME	BRAND NAME	COMPANY	YEAR APPROVED
<b>PROTEASE INHIBITORS (PIs)</b>			
amprenavir	Agenerase	GlaxoSmithKline	1999; discontinued 2004
atazanavir	Reyataz	Bristol-Myers Squibb	2003
fosamprenavir	Lexiva (U.S.); Telzir (Europe)	GlaxoSmithKline	2003
indinavir	Crixivan	Merck	1996
lopinavir/ritonavir	Kaletra	Abbott	2000; Meltrex formulation 2005
nelfinavir	Viracept	Pfizer	1997
ritonavir	Norvir	Abbott	1996
saquinavir	Invirase (hard-gel) Fortovase (soft-gel)	Roche	1995 1997; withdrawn 2005
tipranavir	Aptivus	Boehringer Ingelheim	2005
<b>NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)</b>			
abacavir	Ziagen	GlaxoSmithKline	1998
didanosine (ddl)	Videx	Bristol-Myers Squibb	1989; extended release Videx EC 2000
emtricitabine (FTC)	Emtriva	Gilead	2003
lamivudine (3TC)	Epivir	GlaxoSmithKline	1995
stavudine (d4T)	Zerit	Bristol-Myers Squibb	1994
zalcitabine (ddC)	Hivid	Roche	1992; withdrawn 2005
zidovudine (AZT)	Retrovir	GlaxoSmithKline	1987
tenofovir DF	Viread	Gilead	2002
<b>NRTI FIXED-DOSE COMBINATIONS</b>			
zidovudine/lamivudine	Combivir	GlaxoSmithKline	1997
zidovudine/lamivudine/abacavir	Trizivir	GlaxoSmithKline	2000
lamivudine/abacavir	Epzicom (U.S.); Kivexa (Europe)	GlaxoSmithKline	2004
tenofovir/emtricitabine	Truvada	Gilead	2004
<b>NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)</b>			
delavirdine	Rescriptor	Pfizer	1997
efavirenz	Sustiva (U.S.); Stocrin (elsewhere)	Bristol-Myers Squibb	1998
nevirapine	Viramune	Boehringer Ingelheim	1996
<b>ENTRY/FUSION INHIBITORS</b>			
enfuvirtide (T-20)	Fuzeon	Trimeris	2003

# BETA

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