Bulletin of Experimental Treatments for AIDS

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The statements and opinions in *BETA* are published as an educational resource only, and do not imply recommendation or endorsement by *BETA* or the San Francisco AIDS Foundation. Always consult a physician before starting or modifying any treatment.

editor's note

Depression is a familiar complaint among people living with HIV. Even if physical health has stabilized, symptoms of depression can diminish quality of life and lead to other complications. Lisa Capaldini, MD, and George Harrison, MD, present an overview of this common condition and discuss treatment strategies with HIV positive people in mind (page 18). The current state of research on blood sugar abnormalities—another topical concern—is laid out in "Insulin Resistance and Diabetes" (page 34). Our third feature, "Oral Health and HIV," covers a range of issues from cavities and dry mouth to oral cancers (page 26). Readers will also find an update on tipranavir, a unique protease inhibitor in late-stage development (page 15), and a report on drug resistance in women using antiretroviral agents to prevent mother-to-child HIV transmission (page 32).

We invite our readers to consider the following question for next issue's "In Their Own Words" section: ***What method do you use to stay adherent to your antiretroviral drug regimen?*** *A selection of responses will be published. Please send brief answers to us via e-mail, fax, or post (see our contact information on the facing page).*

Nicholas

In Their Own Words: AIDS advocates

"Given that 2003 saw four new antiretroviral drug approvals—more than any year to date—do you feel that real progress is being made toward a cure for HIV disease?"

Derrick Mapp

"No, not toward a cure. That doesn't mean that we as a global community should give up looking or that something may not show up around the corner. There have been small but incredible advances in our understanding of how this retrovirus operates. But I think that it is easier for the pharmaceutical industry as a business to maintain a cache of nongenerics with enhanced delivery systems rather than actual 'improved' pharmaceuticals. Yes, research and development is difficult, and incremental leaps in medical knowledge are nearly impossible to predict. However, we need to continue pushing for these advances and at pricing levels that benefit all people."

Derrick Mapp is a community advisor for several HIV prevention and treatment research groups. He lives in San Francisco.

Heidi Nass

"Last year we increased our arsenal of really good treatment options, especially for people who have access to medications and don't have any viral resistance to worry about. Unfortunately, even a simple, tolerable, and nontoxic treatment is not a cure. HIV has proven to be a formidable opponent of the best minds, and there are still some basic hurdles to clear before a cure is visible on the horizon. Even so, I fear it will be a continuing lack of political will and financial commitment, not brain power, that will prevent us from winning this war. On my most cynical days, I don't think we'll have a cure until the people and families and communities we lose to AIDS are worth as much as the dollars needed to end the epidemic."

Heidi Nass is an HIV positive community advocate based in Madison, Wisconsin.

Mauro Guarinieri

"I wouldn't say the distance has changed. We have better drugs and we're moving to once-a-day regimens, but a real cure remains as far away as it was last year, and the year before. Progress toward a vaccine is facing ups and downs, and some have already started questioning whether having a vaccine—which is not as mouthwatering as a new blockbuster drug—will ever be possible. Still, the 1996 HAART revolution was real, and those with access to antiretrovirals are privileged enough to deal with quality of life and new emergencies such as cardiovascular risk, coinfections, and even aging. Yet these privileges aren't available to millions of people whose

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NEWS BRIEFS

Liz Highleyman

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

CONFERENCE COVERAGE

Several conferences addressing HIV/AIDS and viral hepatitis have taken place since the previous issue of *BETA*. The 2nd International AIDS Society (IAS) Conference on HIV Pathogenesis and Treatment was held July 13–16 in Paris, preceded by the 5th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV. The 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) was held September 14–17 in Chicago. Others included the 41st Infectious Diseases Society of America (IDSA) annual meeting in San Diego, the 54th American Association for the Study of Liver Disease (AASLD) conference in Boston, and the 9th European AIDS Conference sponsored by the European AIDS Clinical Society (EACS) in Warsaw, all in October 2003. Due to the large volume of information presented at these meetings, *BETA* will cover only selected highlights. See the web sites below for more complete conference coverage.

IAS:
www.ias2003.org
www.hivandhepatitis.com/2003icr/2ndias/main.html
www.thebody.com/confs/ias2003/ias2003.html

Lipodystrophy Workshop:
www.hivandhepatitis.com/2003icr/5thadverse/main.html
www.natap.org/2003/lipo/ndxlipo.htm

ICAAC:
www.icaac.org/ICAAC.asp
www.hivandhepatitis.com/2003icr/43_ICAAC/main.html
www.thebody.com/confs/icaac2003/icaac2003.html

IDSA:
www.idsociety.org/me/am2003/toc.htm
www.hivandhepatitis.com/2003icr/41_IDSA/main.html

AASLD:
www.aasld.org/meetings/annualmeeting/livermeetingbody.htm
www.hivandhepatitis.com/2003icr/03_assld/main.html
www.natap.org/2003/AASLD/ndxAASLD.htm

EACS:
www.eacs.ws
www.hivandhepatitis.com/2003icr/EACS_9/main.html
www.natap.org/2003/EACS/ndxEACS.htm

Best First-Line Regimens

Azra Ghani, PhD, from Imperial College in London (abstract H-849) reported at ICAAC that for people newly starting antiretroviral therapy, regimens containing nevirapine (Viramune), efavirenz (Sustiva), or lopinavir (Kaletra) appear to be the most effective first-line choices. In a retrospective study of 1,119 subjects in the U.S. and the Netherlands between 1999 and 2002, Ghani and colleagues found that those taking nevirapine, efavirenz, or lopinavir were more likely to achieve viral loads under 500 copies/mL than those taking nelfinavir (Viracept) or indinavir (Crixivan) boosted with low-dose ritonavir (Norvir). Those taking efavirenz and nevirapine, both non-nucleoside reverse transcriptase inhibitors (NNRTIs), were also significantly less likely to experience viral rebound than those taking nelfinavir or boosted indinavir. In this study, no significant differences were seen between lopinavir and the two NNRTI regimens in terms of time to virological failure. [Ed. Note: a report in the December 11, 2003 edition of the *New England Journal of Medicine* suggested that AZT (zidovudine, Retrovir)/3TC (lamivudine, Epivir)/efavirenz is the best first-line regimen.]

Protease Inhibitors

At the IAS conference, Bonaventura Clotet, MD, PhD, of Hospital Universitari Germans Trias i Pujol in Badalona (abstract 118) reported that a regimen containing atazanavir (Reyataz) boosted with low-dose ritonavir compares favorably to lopinavir (the Kaletra pill is formulated with a small dose of ritonavir). Dr. Clotet and colleagues found that among 358 treatment-experienced subjects without high-level protease inhibitor (PI) resistance, a 24-week interim analysis revealed that viral suppression and CD4 cell increases were similar in the atazanavir and lopinavir arms (viral load less than 400 copies/mL in 64% and 62%,

and less than 50 copies/mL in 39% and 42%, respectively); less antiviral activity was seen in those taking atazanavir plus saquinavir (Fortovase or Invirase). Subjects taking atazanavir had lower total cholesterol, LDL ("bad") cholesterol, and triglyceride levels, but higher HDL ("good") cholesterol compared with those taking lopinavir. Atazanavir is advantageous because it can be taken once daily (although this may also prove possible with lopinavir, as noted below).

In a late-breaker presentation at the same meeting, Mike Youle, MD, of the Royal Free Hospital in London (abstract LB23) reported final results from the MaxCMin2 study comparing different PI regimens. Dr. Youle and colleagues found that among more than 300 subjects (27% treatment-naive, 73% treatment-experienced, 32% with prior PI failure), those taking lopinavir achieved greater viral suppression than those taking saquinavir/ritonavir after 48 weeks (60% vs 53%, respectively, with viral loads below 50 copies/mL). In addition, nearly twice as many in the saquinavir/ritonavir arm discontinued due to adverse side effects. Also at the IAS conference, Charles Flexner, MD, of Johns Hopkins University in Baltimore (abstract 843) reported that higher doses of lopinavir may be able to overcome PI resistance. His results suggest that taking more Kaletra combination pills may work better than adding more ritonavir to boost lopinavir levels.

Challenging the standard rule that antiretroviral therapy should always include more than one drug, Joseph Gathe, MD, from Therapeutic Concepts in Houston (abstract H-845) presented controversial data at ICAAC from a study of lopinavir "monotherapy" (although, as noted above, the Kaletra pill contains a low dose of ritonavir). Dr. Gathe and colleagues found that among 22 treatment-naive subjects with a wide range of viral load levels and CD4 cell counts who completed 24 weeks of therapy with lopinavir alone, only one did not achieve a viral load under 400 copies/mL; about half had viral loads below 50 copies/mL. The one subject who did not achieve an undetectable viral load started with a high HIV RNA level (500,000 copies/mL) and dropped to about 1,500 copies/mL. It is hypothesized that because lopinavir reaches high concentrations in the blood, it is less likely to promote the development of resistance. In this study, only one genotypic resistance mutation and no evidence of phenotypic resistance was seen. Solo lopinavir "exhibited virological efficacy comparable to triple therapy," Dr. Gathe concluded.

In other lopinavir news, at the October EACS meeting Daniel Podzamczer, MD, from Hospital Universitario de Bellvitge in Barcelona (abstract F1/3) reported data suggesting that it may be possible to use the drug just once daily. In a pilot study of 190 subjects randomized to receive 800/200 mg lopinavir/ritonavir once daily or 400/100 mg lopinavir/ritonavir twice daily, the two dosing schedules appeared comparably effective at 24 weeks. Using an intent-to-treat analysis, 57% in both arms achieved viral loads below 50 copies/mL; in an as-treated analysis, the rates were 68% and 70% for the once-daily and twice-daily arms, respectively. Among the smaller number of subjects followed for 32 weeks, the corresponding as-treated rates were 82% and 81%. However, 11% discontinued due to adverse events in the once-daily arm, compared with only 3% in the twice-daily arm.

Finally, at ICAAC, Joseph Eron, MD, from the University of North Carolina at Chapel Hill (abstract H-844) presented data from a study of 100 subjects who had taken lopinavir for more than five years. About two-thirds maintained undetectable viral loads after 252 weeks (67% under 400 copies/mL, 64% under 50 copies/mL) and none of these developed resistance.

Other Antiretrovirals

Researchers at IAS presented results from Gilead Science's Phase III study 903 showing that tenofovir DF (Viread) is as effective as d4T (stavudine, Zerit), but is associated with fewer adverse side effects. Anton Pozniak, MD, from Chelsea and Westminster Hospital in London and colleagues (abstract 559) randomized study subjects to receive tenofovir or d4T (both with 3TC and efavirenz). After 96 weeks, an intent-to-treat analysis including 600 subjects found that the two regimens had similar efficacy: 82% in the tenofovir arm and 78% in the d4T arm achieved viral loads below 400 copies/mL.

However, according to an analysis by Schlomo Staszewski, MD, from Goethe-Universität in Frankfurt and colleagues (abstract 562), participants receiving tenofovir had less elevated triglyceride, total cholesterol, and LDL cholesterol levels, and also experienced less wasting of fat in the limbs (lipoatrophy). In addition, Joel Gallant, MD, from Johns Hopkins presented data at ICAAC from the same study (abstract H-840) showing that tenofovir does not appear to cause more kidney toxicity than d4T—a potential concern since there have been several reported cases of kidney damage in people taking tenofovir. In this study, subjects in the tenofovir and d4T arms had similar rates of biochemical abnormalities associated with kidney toxicity. Nevertheless, tenofovir should be used with caution and doses should be adjusted in people with pre-existing kidney dysfunction (see item on tenofovir label changes, below).

At the Paris lipodystrophy workshop, Andrew Carr, MD, from St. Vincent's Hospital in Sydney (abstract 16) presented data from another study that cast a shadow over d4T. Dr. Carr and colleagues found that after two years, individuals who switched from d4T to abacavir (Ziagen) regained about one-third of lost limb fat, while visceral abdominal fat did not change.

Therapy for heavily treatment-experienced individuals remains a major challenge in HIV medicine. At ICAAC, Jean-Michel Molina, MD, PhD, from Hôpital Saint-Louis in Paris (abstract H-447) reported that adding ddI (didanosine,

Videx) to a failing regimen could produce significant reductions in viral load. In the Jaguar study, Dr. Molina and colleagues found that about one-third (33 out of 111) of treatment-experienced subjects with viral loads between 1,000 and 100,000 copies/mL despite therapy achieved undetectable viral loads (below 400 copies/mL) four weeks after adding ddI to their regimens, compared with about 5% (3 out of 58) who added a placebo. This benefit was seen despite the fact that a majority of the subjects had previously used ddI. (Research from IAS and ICAAC on the unexpectedly poor showing of triple-NRTI regimens is covered in a news item below.)

Finally, looking at the newest class of antiretroviral drugs, Benoit Trottier, MD, from Clinique l'Actuel in Montreal (H-835) presented data from the TORO 1 and TORO 2 studies at ICAAC showing that treatment-experienced individuals can continue to benefit from T-20 (enfuvirtide, Fuzeon). At 48 weeks, about one-third (201 out of 661) of subjects receiving T-20 plus an optimized background regimen maintained or achieved viral loads below 400 copies/mL. Eighty percent of those who had achieved viral suppression at 24 weeks continued to benefit, along with five new responders. However, it is known that HIV can develop resistance to T-20. At the same conference, Jay Lalezari, MD, of Quest Clinical Research in San Francisco (H-444) reported data on T-1249, a second-generation entry inhibitor that binds to a different section of HIV's gp41 envelope protein and works against T-20–resistant virus. Dr. Lalezari and colleagues found that among 53 subjects with viral loads between 5,000 and 500,000 copies/mL while taking T-20, about three-quarters experienced at least a 1 log (90%) decrease in HIV RNA (mean 1.26 logs) ten days after switching to T-1249. No serious adverse side effects were reported, although injection site reactions were common. [Ed. Note: in early January 2004, trials of T-1249 were stopped due to problems with the drug's formulation.]

Once-Daily Regimens

Study results continue to confirm that once-daily regimens are the cutting edge of HIV treatment. In a late-breaker presentation at ICAAC, Brian Gazzard, MD, from Chelsea and Westminster Hospital (abstract H-1722b) reported results from the ZODIAC study showing that once-daily abacavir appears safe and effective. The current recommended abacavir dosing schedule is one 300 mg tablet twice daily; Dr. Gazzard and colleagues tested a once-daily 600 mg dose. Among the 770 participants in this study, 66% of those who received once-daily abacavir achieved viral loads below 50 copies/mL at 48 weeks, compared with 68% of those taking abacavir twice daily. In both arms, about 10% experienced viral rebound. Subjects in the once-daily arm gained 188 CD4 cells/mm^3, compared with 200 cells/mm^3 in the twice-daily arm. The percentages experiencing an abacavir hypersensitivity reaction were similar in both arms. The researchers concluded that once-daily abacavir offers "an important new treatment simplification option." GlaxoSmithKline is currently working on a once-daily combination pill containing abacavir plus 3TC.

As Edwin DeJesus, MD, from IDC Research in Altamonte Springs reported at the same conference (abstract H-446), in a large, multicenter Phase III study (CNA30024) abacavir/3TC/efavirenz suppressed HIV replication as well as AZT/3TC/efavirenz (viral loads below 50 copies/mL in 70% and 69%, respectively), but those in the abacavir arm experienced greater CD4 cell increases (209 vs 155 cells/mm^3). Dr. Gazzard's and Dr. DeJesus' data together suggest that abacavir/3TC/efavirenz may be an effective, completely once-daily regimen.

Treatment Interruption

Treatment interruption remains controversial, although a consensus is emerging that treatment breaks seem to provide little or no benefit and may, in fact, be harmful. For example, at the IAS meeting Bernard Hirschel, MD, of Geneva University Hospital in Switzerland (abstract LB04) reported data from the Staccato study showing that subjects who received treatment in one-week-on, one-week-off cycles were more likely to experience virological failure. More than half the cycling subjects (19 out of 36) had two successive viral load measurements over 500 copies/mL after the completion of an off-treatment week. The one-week-on, one-week-off schedule "showed an unacceptably high failure rate," according to the researchers, and was therefore halted.

In the August 28, 2003 issue of the *New England Journal of Medicine*, Jody Lawrence, MD, of the University of California at San Francisco (UCSF) and colleagues also reported that treatment interruptions may be harmful. In CPCRA study 064, participants with multidrug-resistant HIV and viral loads above 5,000 copies/mL were randomly assigned to interrupt treatment for four months before starting a new regimen or to start a new regimen immediately. Disease progression or death occurred in about 16% of subjects (22 out of 138) in the delayed change arm compared with about 9% (12 out of 132) in the immediate change arm. Those in the treatment interruption arm also had lower CD4 cell counts. "In patients infected with multidrug-resistant HIV, structured interruption of treatment was associated with greater progression of disease and did not confer immunologic or virologic benefits or improve the overall quality of life," the authors concluded. Said Anthony Fauci, MD, of the National Institute of Allergy and Infectious Diseases, "The general message from this study is if you have drug-resistant virus, stopping therapy does not help, period, because the virus rebounds and the infection progresses."

Yet treatment discontinuation may be appropriate under certain circumstances, particularly if therapy was started with a high CD4 cell count, when it may not have been needed in the first place. Franco Maggiolo, MD, from Ospedali Riuniti in Bergamo (H-448) reported data from

the BASTA study at ICAAC. In this trial, 114 subjects with CD4 cell counts above 800 cells/mm^3 and undetectable viral loads while on highly active antiretroviral therapy (HAART) were randomized to stop (76 participants) or continue therapy (38 participants). Treatment was restarted when an individual's CD4 cell count fell below 400 cells/mm^3. Overall, 21% resumed therapy during the 18-month follow-up period. Dr. Maggiolo and colleagues found that the nadir (lowest ever) CD4 cell count predicted how much time elapsed before treatment was restarted. Those with CD4 nadirs below 200 cells/mm^3 restarted in about seven months, compared with about 14 months for those with nadirs of 200–350 cells/mm^3 and about 18 months for those with nadirs of 350–500 cells/mm^3. No one with a CD4 nadir above 500 cells/mm^3 had to resume therapy.

In another interesting treatment strategy study, Javier Martínez-Picado, PhD, from Hospital Universitari Germans Trias i Pujol reported at the IAS meeting (abstract LB05) and in the July 15, 2003 issue of the *Annals of Internal Medicine* that individuals who alternated between two different HAART regimens maintained virological suppression longer than those who took either regimen continuously. In the SWATCH study, 161 participants from Spain and Argentina were randomized to receive 3TC/ddI/efavirenz or 3TC/AZT/nelfinavir continuously, or to alternate between the two regimens every three months. Subjects receiving the two continuous regimens had similar rates of virological suppression, but virological failure was delayed in those who alternated regimens. Participants in all three arms had similar CD4 cell counts and rates of adverse side effects.

Resistance and Superinfection

At the IAS meeting, David van de Vijver, MD, from the University Medical Center in Utrecht (abstract LB01) reported that nearly 10% of 1,633 newly diagnosed HIV positive subjects in the CATCH cohort (from 16 European countries and Israel) were resistant to at least one antiretroviral drug, even though they had never been treated for HIV. Infection with resistant virus was higher among those most recently infected; those who seroconverted (became HIV positive) within the previous year had a resistance rate of nearly 11%, compared with a 7.5% resistance rate among those infected for more than a year. By drug class, 6.9% were resistant to nucleoside reverse transcriptase inhibitors (NRTIs), 2.6% were resistant to NNRTIs, 2.2% showed PI resistance, and 1.7% were resistant to two or more classes. Resistance rates were highest among those with subtype B HIV, the most prevalent type in Europe and the U.S.

There were also several presentations at IAS concerning HIV superinfection, in which a person infected with one strain of the virus subsequently contracts another strain (it may also refer to simultaneous infection with more than one strain, also known as coinfection). Luc Perrin, MD, from University Hospital in Geneva (abstract 73) reported on five injection drug users (out of a cohort of 136) who experienced sudden increases in viral load. Two of these had previously controlled their infections without therapy, maintaining viral loads below 50 copies/mL and CD4 cell counts above 500 cells/mm^3, but experienced sudden viral load escalations and rapid CD4 cell declines—common manifestations of initial HIV infection—upon infection with a second strain of HIV. According to reports from other researchers, coexisting strains of HIV can recombine to form hybrid strains. Harold Burger, MD, from Albany Medical College (abstract 71), for example, reported on a hybrid subtype A/subtype C strain detected in a female sex worker from Kenya.

Experimental Drugs

Progress on several experimental drug candidates was reported at the IAS and ICAAC meetings, with attention focusing on new entry inhibitors. Dr. Pozniak (abstract H-443) presented results at ICAAC from a short-term study of Pfizer's CCR5 chemokine blocker, UK-427,857. Antiviral activity was seen in 24 asymptomatic HIV positive subjects treated for ten days, with a mean viral load decrease of 1.42 logs in the arm receiving 100 mg and 0.42 logs in the 25 mg arm. Higher drug levels where achieved when the drug was taken without food. As expected, UK-427,857 was active only against HIV that uses the CCR5—not the CXCR4—coreceptor to enter cells. In a study of UK-427,857 safety in HIV negative volunteers, D. Russell from Pfizer and colleagues (abstract H-874) found that the agent (at doses of 100 mg or 300 mg twice daily) was well tolerated and produced no serious adverse effects after 28 days. In particular, no heart rhythm abnormalities were seen—as they were in studies of a previous CCR5 blocker candidate—and there were no significant changes in blood lipids (fats).

Finally, R.J. Hazen from GlaxoSmithKline (abstract H-445) reported on GW8248, an experimental benzophenone NNRTI. This agent was active against HIV with NNRTI-resistance mutations, including K103N and Y181C, which confer resistance to all the currently approved drugs in this class. However, researchers were able to grow GW8248-resistant HIV in the laboratory.

NEW DRUG APPROVALS

With a total of four, 2003 saw more new antiretroviral drug approvals than any year to date. As noted in the Summer 2003 issue of *BETA*, the U.S. Food and Drug Administration (FDA) approved the first entry inhibitor—T-20 (enfuvirtide, Fuzeon)—in March, and a new PI, atazanavir (Reyataz) in June. Atazanavir is noteworthy because it is the first once-daily PI and appears less likely to increase blood lipid levels than other drugs in its class.

On July 2 the FDA gave the nod to FTC (emtricitabine, Emtriva), a new NRTI manufactured by Gilead. FTC is structurally similar to 3TC and shares a similar resistance profile, although it remains longer in the body. Studies to date have shown that the drug is well tolerated; the most

common adverse side effects are skin discoloration (especially in people of color), nausea, diarrhea, headache, and skin rash. Gilead is currently testing a once-daily combination pill that contains FTC plus tenofovir. FTC is also active against the hepatitis B virus (HBV)—as is 3TC—but it has not yet been approved for this indication. For complete FTC prescribing information, see **www.emtriva.com.**

On October 22 the FDA approved another new PI, fosamprenavir, to be marketed as Lexiva. The drug (formerly known as GW433908, or simply 908) is a prodrug of amprenavir (Agenerase). It is produced through a partnership between GlaxoSmithKline and Vertex Pharmaceuticals. The drug was approved based on three studies: NEAT (APV30001) and SOLO (APV30002) in treatment-naive individuals, and CONTEXT (APV30003) in treatment-experienced people. In the NEAT trial, 57% of those taking fosamprenavir and 42% of those taking nelfinavir achieved viral loads below 50 copies/mL after 48 weeks. In the SOLO study, which used ritonavir-boosted fosamprenavir, the corresponding percentages were 58% and 55%. In the CONTEXT trial, 46% of those receiving fosamprenavir/ritonavir achieved viral loads below 50 copies/mL after 48 weeks, compared with 50% of those taking lopinavir/ritonavir. Fosamprenavir has a low pill burden—just 2–4 capsules per day—with no food restrictions. Treatment-naive individuals may take the drug once daily, but twice-daily administration is recommended for treatment-experienced people. The most common side effects of fosamprenavir are nausea, diarrhea, headache and skin rash, generally mild to moderate in severity. For complete prescribing information, see **www.lexiva.com.**

On the opportunistic illness (OI) front, the FDA in November approved voriconazole, to be marketed as VFEND, a new broad-spectrum antifungal drug for the treatment of esophageal candidiasis (thrush). In a clinical trial involving immunocompromised participants in 15 countries, voriconazole was about as effective as fluconazole (Diflucan). (For more information on thrush, see page 28.)

Finally, in October, the FDA granted "fast track" status to Tanox, Inc.'s experimental monoclonal antibody, TNX-355. One of a new type of pharmaceutical known as biologics, TNX-355 works by binding to host cell CD4 receptors and preventing HIV from entering cells. Fast track status allows for expedited review by the regulatory agency, and Tanox may submit clinical trial data as soon as they become available rather than waiting until all studies are completed.

NRTI-ONLY REGIMENS: CAUTION!

Evidence continues to accumulate that regimens containing only nucleoside and/or nucleotide reverse transcriptase inhibitors may not be sufficiently potent in most people with HIV. As reported in the Summer 2003 issue of *BETA*, one arm of ACTG study 5095 was halted in March after early results showed that people taking only Trizivir (the AZT/3TC/abacavir combination pill) achieved inferior viral suppression compared with those who took efavirenz plus Combivir (AZT/3TC). Data from ACTG 5095 were presented at the IAS meeting, and at ICAAC researchers from Madrid (abstract H-838) reported data confirming that AZT/3TC/abacavir is less potent than regimens that contain either efavirenz or nevirapine plus AZT/3TC (78% taking AZT/3TC/abacavir and 95% taking one of the NNRTIs achieved viral loads below 50 copies/mL in an as-treated analysis). Some physicians continue to prescribe solo Trizivir for selected patients due to its convenience—only two pills daily—but the most recent U.S. HIV treatment guidelines (see below) do not recommend this regimen for people with viral loads above 100,000 copies/mL.

Other NRTI-only combinations also came under fire in the summer of 2003. At the IAS meeting, Charles Farthing, MD, of the AIDS Healthcare Foundation in Los Angeles reported viral rebound in 52% (9 out of 17) of treatment-naive individuals receiving once-daily tenofovir/abacavir/3TC. Dr. Gallant provided further data on this regimen in a late-breaker session at ICAAC (H-1722a). In study ESS30009, Dr. Gallant and colleagues randomized 194 participants to receive either tenofovir/abacavir/3TC or efavirenz/abacavir/3TC once daily. After several cases of early virological failure were reported, an unplanned interim analysis revealed that 49% (50 out of 102) in the tenofovir arm experienced treatment nonresponse or failure (less than a 2 log decrease in HIV RNA or viral rebound after successful suppression) by eight weeks, compared with just 5.4% (5 out of 92) in the efavirenz arm. Results were similar in the smaller number of subjects treated for 12 weeks. Only about one-third of those receiving tenofovir achieved viral loads under 50 copies/mL by week 8, compared with 95% of those taking efavirenz. More than half the subjects in the tenofovir arm developed both the K65R tenofovir-resistance mutation and the M184V 3TC-resistance mutation. The study was halted and GlaxoSmithKline sent an advisory letter to physicians on July 25. "Abacavir and lamivudine [3TC] in combination with tenofovir should not be used as a triple antiretroviral therapy when considering a new treatment regimen for naive or pretreated patients," the letter stated. "Any patient currently controlled on therapy with this combination should be closely monitored and considered for modification of therapy."

On October 14 Gilead Sciences also issued a letter to physicians warning of high failure rates with yet another triple NRTI regimen, tenofovir/ddI/3TC. In a pilot study of 21 treatment-naive participants, 91% of those taking this regimen once daily were unable to suppress viral replication after 24 weeks. Again, half developed both the K65R and M184V mutations. Enrollment in this study was also halted. "Tenofovir in combination with didanosine [ddI] and lamivudine [3TC] is not recommended when considering a

new treatment regimen for therapy-naive or experienced patients with HIV infection," stated the letter. "Patients currently on this regimen should be considered for treatment modification."

It is not yet clear why failure rates are so high with these triple-NRTI combinations. As noted above, study results to date suggest that once-daily abacavir appears to be effective. Laboratory studies did not indicate drug interactions between tenofovir and other NRTIs, although this may be occurring on a cellular level. The two tenofovir-containing triple-NRTI regimens appear to have a "low genetic barrier," meaning HIV easily develops resistance to these drugs used in combination. However, treatment failure occurred even in some study subjects who did not show evidence of resistance mutations. And while tenofovir and abacavir share the K65R resistance mutation, tenofovir and ddI do not have similar resistance profiles. Until more is known, tenofovir/abacavir/3TC and tenofovir/ddI/3TC should not be used as triple combination regimens. However, tenofovir and abacavir may be used together in combination with other drugs.

TENOFOVIR LABEL CHANGES

In August the FDA approved new product labeling information for tenofovir DF (Viread). The new label includes data on the use of the drug in treatment-naive individuals from study 903 (described above); the drug was initially approved in October 2001 based on data from treatment-experienced people. The revised label also includes dose recommendations when tenofovir is used with ddI and a warning about use of tenofovir in people with HBV coinfection. Because kidney problems have been reported in several people taking tenofovir, the new label recommends adjusted doses and careful monitoring (including urine testing for the presence of proteins) in people with pre-existing kidney impairment. There is also updated information on the drug's effect on bone mineral density. In study 903, after 48 weeks, individuals receiving tenofovir had greater bone mineral loss than those taking d4T, as well as higher levels of biochemical markers associated with bone loss. Finally, the new label indicates that tenofovir may be taken with or without food (the original label recommended taking it with a meal). The revised product information is available at **www.viread.com.**

In related news, French researchers reported in the December 15, 2003 issue of *Clinical Infectious Diseases* on several cases of severe multiple toxicities when tenofovir was combined with Kaletra and ddI. The researchers suggested that the ritonavir in Kaletra increased tenofovir concentrations, leading to kidney dysfunction, while tenofovir increased ddI levels, leading to peripheral neuropathy.

FLUMIST WARNING

According to the Centers for Disease Control and Prevention (CDC), the new live attenuated intranasal flu vaccine (FluMist) approved in June may not be safe for people with HIV. Because the virus is live, it can potentially spread from recently vaccinated people to others with whom they come in contact. Until more is known, the CDC recommends against the use of FluMist by immunocompromised individuals—including those with HIV—and people who have regular contact with them (such as health-care workers and family members). The older, injected influenza vaccine is still considered safe, and is recommended for people with HIV.

REVISED TREATMENT GUIDELINES

The U.S. Department of Health and Human Services (DHHS) updated the federal guidelines for HIV treatment in adults and adolescents on July 14 and again on November 10, 2003. Unlike many past revisions, which often made only minor alterations, the July update completely changed how the guidelines are presented (although the recommendations themselves do not differ dramatically). Replacing the old "one from column A, two from column B" approach—which has become increasingly cumbersome as the number of approved antiretroviral drugs has grown—the new guidelines recommend two specific preferred first-line regimens:

efavirenz + 3TC + AZT or d4T or tenofovir

lopinavir + 3TC + AZT or d4T

Stressing the importance of individualized therapy, the guidelines also include several alternative regimens and a chart outlining the benefits and drawbacks of different drugs. The guidelines also include revised discussions of treatment failure, selection of new regimens, treatment interruption, and therapeutic drug monitoring.

The inclusion of d4T as part of a preferred regimen provoked controversy due to the drug's association with lipoatrophy and mitochondrial toxicity. Some experts also raised eyebrows over the inclusion of a triple-NRTI regimen (AZT/3TC/abacavir, or Trizivir) for treatment-naive individuals with viral loads under 100,000 copies/mL, given recent data (described above) showing that NRTI-only regimens appear insufficiently potent.

The November version provided some clarifications and revisions to the July update. These included an explanation of the difference between "preferred" and "alternative" regimens, as well as the addition of atazanavir as an alternative PI and FTC as an alternative NRTI (although fosamprenavir is still omitted). Based on the recent unfavorable data described above, two triple-NRTI regimens—tenofovir/abacavir/3TC and tenofovir/ddI/3TC—were added to the list of regimens that "should not be offered at any time."

On November 26, 2003, the U.S. government also issued updated guidelines for anti-HIV therapy in pregnant women. Overall, treatment for pregnant women is similar to that for other people with HIV. However, certain drugs

(i.e., AZT or nevirapine) are recommended to prevent mother-to-child transmission, while other agents should be avoided due to their association with adverse birth outcomes (e.g., efavirenz) or used with caution due to a higher risk of side effects (e.g., d4T and ddI in combination).

Both the revised adult and adolescent guidelines and the recommendations for pregnant women can be found at **www.aidsinfo.nih.gov/guidelines.**

In related news, the HIV Medicine Association of the Infectious Diseases Society of America and the Adult AIDS Clinical Trials Group (AACTG) released guidelines for managing elevated lipid levels associated with antiretroviral therapy, published in the September 1, 2003 issue of *Clinical Infectious Diseases.* As a first step, the guidelines recommend a reduced-fat diet, weight loss (if indicated), aerobic and resistance exercise, and smoking cessation. If these measures are not adequate, the guidelines recommend pravastatin (Pravachol) or atorvastatin (Lipitor) for elevated LDL cholesterol, and gemfibrozil (Lopid) or fenofibrate (Tricor) for elevated cholesterol accompanied by elevated triglycerides. However, the panel noted that lipid-lowering agents have not been studied extensively in people with HIV, and some are known to interact with antiretroviral medications. [Ed. Note: the new statin drug rosuvastatin (Crestor) appears not to interact with anti-HIV drugs and compares favorably with other statins in terms of potency.]

HAART REDUCES DEATH RATE

According to a report in the October 18, 2003 issue of *The Lancet*, use of HAART has reduced the rate of death in people with HIV by more than 75%. Kholoud Porter, MD, of the British Medical Research Council in London and a large team of colleagues representing 22 cohort studies in Europe, Australia, and Canada—a total of more than 7,700 seroconverters—reported that the AIDS-related death rate had decreased by 50% by 1997 (the year after PIs were widely introduced) and by 80% by 2001. Today, most people receiving potent antiretroviral therapy live for more than a decade, and possibly much longer (less than a decade has passed since the introduction of effective HAART, so the upper limit is not yet known). Individuals who were older when they seroconverted did not appear more likely to die than those who seroconverted at younger ages. This contrasts with the pre-HAART era, when people who were infected at age 45 or older had lower life expectancies than those diagnosed at younger ages. However, injection drug users who contracted HIV through shared needles were four times more likely to die of AIDS-related causes than men infected through sexual transmission, a difference that was not apparent before HAART became available. "Before, age mattered, now it doesn't. Before, exposure category or risk group didn't matter and now it does," said Dr. Porter.

In less promising news, Carl Fichtenbaum, MD, of the University of Cincinnati reported at the October EACS meeting that since HAART has reduced mortality due to AIDS-related OIs, cardiovascular disease and liver problems have become major causes of hospitalization and death among HIV positive people receiving treatment—a concern because these conditions have been linked to antiretroviral therapy. Based on an analysis of data from several managed health plans in 2000 and 2001 (including a total of 756 subjects), Dr. Fichtenbaum and colleagues found that cardiac, vascular, and/or atherosclerotic (hardening of the arteries) disease were among the most frequent reasons for hospital admission (8.5%). Other common causes were kidney problems (5.8%), liver toxicity (5.6%), and blood cell deficiencies (5.0%). OIs accounted for only 3.4% of hospital admissions.

SEVERE SIDE EFFECTS MORE LIKELY THAN ADVANCED AIDS

According to a report in the December 1, 2003 issue of the *Journal of Acquired Immune Deficiency Syndromes,* HIV positive people on HAART are about twice as likely to experience severe drug side effects as AIDS-defining conditions. The study included data from 2,947 participants collected between 1996 and 2001. By the 12th month of follow-up, 89% were receiving HAART (70% used a PI-based regimen and 19% used an NNRTI-based regimen). Severe (grade 4) side effects were seen in 675 subjects, while 332 developed AIDS-defining conditions; 272 individuals died during the study, 159 of whom developed both a severe adverse drug reaction and an AIDS-defining condition. Among those with severe side effects, liver toxicity was most common, and was associated with hepatitis B or C coinfection. The authors recommend that physicians should carefully assess their patients' medical history for preexisting medical problems before prescribing anti-HIV therapy in order to reduce the risk of serious adverse events.

ADHERENCE MORE IMPORTANT THAN CD4 CELL COUNT

In the November 18, 2003 issue of the *Annals of Internal Medicine,* Evan Wood, PhD, and colleagues from the University of British Columbia in Vancouver reported that anti-HIV therapy can safely be delayed until CD4 cell count falls to 200 cells/mm^3. However, once they start treatment, individuals must maintain good adherence in order to benefit from therapy. The HAART Observational Medical Evaluation and Research (HOMER) study included 1,422 participants who started combination anti-HIV therapy between 1996 and 2000. Among individuals who maintained at least 75% adherence, those who started treatment with a CD4 cell count of 200 cells/mm^3 were as likely to survive as those who started with a CD4 cell count of 350 cells/mm^3 or higher (a mortality rate of about

7%). However, those who achieved less than 75% adherence had a mortality rate more than twice as high (about 15%). The latest U.S. treatment guidelines recommend starting therapy when the CD4 cell count falls to 350 cells/mm^3. But this study suggests that adherence is more important than when HAART is initiated. Subjects who achieved poor adherence had more than double the mortality rate even if they started treatment with a CD4 cell count of 350 cells/mm^3 or higher.

HAART MAY NOT PREVENT BRAIN DAMAGE

Antiretroviral therapy may not prevent brain damage related to HIV, even if it reduces blood viral load, according to a study in the November 14, 2003 issue of *NeuroReport*. Linda Chao, PhD, and colleagues from UCSF and the San Francisco Veterans Affairs Medical Center administered neuropsychological tests measuring psychomotor speed, selective attention, and mental flexibility to 39 asymptomatic HIV positive subjects (23 with detectable and 16 with undetectable viral loads) and 39 HIV negative control subjects. They also recorded brainwaves during a reaction time test to gauge contingent negative variation (CNV), an estimate of alertness and preparation to initiate motor activity. In addition, magnetic resonance imaging (MRI) was used to measure the size of various brain structures in 31 HIV positive and 35 HIV negative subjects.

Overall, the participants with HIV showed poorer results. On the neuropsychological tests, HIV positive and HIV negative subjects generally performed about equally well, but on three tests HIV positive subjects with detectable viral loads did worse than either HIV positive subjects with undetectable virus or HIV negative controls. In the CNV test, a surge of brainwave activity was seen in HIV negative but not in HIV positive subjects, although the participants had similar response times regardless of HIV status. Weaker brainwave activity is associated with damage to the basal ganglia, a cluster of nerve cells in the lower part of the brain that controls motor behavior and is known to harbor HIV. MRI scans revealed that the thalamus, which coordinates sensory input, was smaller in HIV positive subjects regardless of viral load.

AIDS-related dementia (including memory loss, cognitive impairment, and vision, speech, and motor deficits) was once common in people with HIV disease, but the rate has fallen since the advent of HAART. However, this study suggests that subtle neurological damage may still be occurring despite anti-HIV therapy—damage too subtle to be noticed while performing everyday tasks. “Antiviral medications might not be stopping brain damage,” said Dr. Chao. “When we put patients’ brains under closer scrutiny, we saw that they were affected.” It is unclear whether damage to the subjects’ brains occurred before or after beginning anti-HIV therapy. Since most antiretroviral drugs do not cross the blood-brain barrier, a natural filter that protects the brain from harmful agents, HIV may be present in the brain even if it is undetectable in the blood.

NEW DATA ON CARDIOVASCULAR RISK

Three recent reports add to the evidence that antiretroviral therapy contributes to an increased risk of cardiovascular disease in people with HIV.

In the August 1, 2003 issue of the *Journal of Acquired Immune Deficiency Syndromes,* Judith Currier, MD, from the University of California at Los Angeles (UCLA) and colleagues reported that among more than three million people in the California state Medicaid (Medi-Cal) program—more than 28,000 of whom had HIV—the incidence of coronary heart disease (CHD) was significantly higher in HIV positive men in the 18–24 age category, an age at which people do not commonly develop heart disease. CHD rates were higher in HIV positive women in both the 18–24 and 35–44 age groups, although it was lower in the over-44 age group. CHD was associated with antiretroviral therapy among those aged 18–33, but not in the other age groups.

In the November 20, 2003 issue of the *New England Journal of Medicine*, researchers reported further results from the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study, the largest prospective trial designed to analyze cardiovascular risk factors in people with HIV. The DAD Study Group collected data from 23,486 HIV positive participants in the U.S., Europe, and Australia between 1999 and 2002; 75% had taken combination antiretroviral therapy (most had taken PIs), 74% were men, more than half were current or past smokers, and the average age was 39. After an average follow-up period of 1.5 years, 126 heart attacks (myocardial infarctions, or MIs) were recorded, of which 36 were fatal. Use of HAART was associated with a 26% relative increase in the heart attack rate per year of antiretroviral drug exposure; that is, the risk increased with longer duration of anti-HIV therapy. The authors suggested that the increased risk was due to elevated total cholesterol and triglyceride levels associated with PIs. There was no evidence that longer duration of HIV infection or higher viral load was associated with increased heart disease risk. The absolute rate of MI was low—about one per 250 individuals taking HAART for four years—and the researchers concluded that “the substantial benefits of combination antiretroviral therapy continue clearly to outweigh the increased risk of myocardial infarction associated with this therapy.”

In the November 21, 2003 issue of *AIDS*, Murielle Mary-Krause, PhD, from INSERM in Paris and colleagues also reported that the risk of heart attack increased with duration of PI use. The researchers analyzed data from 34,976 men in the French Hospital Database on HIV from 1996 through 1999. During this period, 66 MIs were recorded, 49 of them in individuals taking PIs. Comparing this with the rate among HIV negative French men, the researchers concluded that the risk of MI was higher in people who had been exposed to PIs for longer periods; among those who had used a PI for more than 30 months,

the MI rate was three times that of the general population. Other classes of anti-HIV drugs were not associated with increased MI risk. Here, too, the absolute MI rate was low, and the authors concluded that "the increase in life expectancy conferred by HAART clearly outweighs the associated risk of MI."

In an editorial accompanying the DAD article, Peter Sklar, MD, MPH, of Drexel University College of Medicine and Henry Masur, MD, of the National Institutes of Health (NIH) provided an overview of various studies of HAART and cardiovascular risk, including one by Samuel Bozzette, MD, of the University of California at San Diego showing a decrease in hospitalizations and deaths due to heart attack and stroke in more than 36,000 HIV positive veterans since the advent of PIs. Drs. Sklar and Masur concluded that "the weight of the evidence" indicates that HIV positive people treated with combination antiretroviral therapy are at increased risk for the development of premature atherosclerosis, a known risk factor for cardiovascular disease. They added that lifestyle changes, smoking cessation, and lipid-lowering medications (if indicated) are "logical" and "prudent" steps to reduce the risk of having a heart attack. Peter Reiss, MD, of the University of Amsterdam reached a similar conclusion in an editorial accompanying the Mary-Krause article. "For the time being, the overall absolute risk of premature CAD [coronary artery disease] in HIV-1 infected patients treated with combination ART [antiretroviral therapy] is likely to be only moderately increased," he wrote. "Clearly this does not outweigh the marked benefit which such treatment confers in terms of reducing HIV-1–associated morbidity and mortality."

BONE LOSS LINKED TO HIV, NOT THERAPY

Bone loss is associated with HIV infection itself, not antiretroviral therapy, according to a study in the September 5, 2003 issue of *AIDS*. Dario Bruera, MD, from the National University of Córdoba, Argentina, and colleagues analyzed data from 111 HIV positive and 31 HIV negative subjects; among those with HIV, 33 had never used antiretroviral therapy, 36 had more than one year of treatment without a PI, and 42 had more than one year of treatment including a PI. Bone mineral density (lumbar spine, femur, and total body) was significantly lower in the HIV positive subjects compared with the HIV negative subjects, and the incidence of osteopenia and osteoporosis (below average and severely low bone density) was higher in the former group. Those who had been infected with HIV the longest were at greatest risk for bone loss. However, among the HIV positive participants, no differences were seen based on presence or type of antiretroviral therapy. The results suggest that HIV itself has an adverse effect on bone density, the researchers concluded. (For more information, see "Osteoporosis and HIV Disease," *BETA*, Summer/Autumn 2001; and "Osteonecrosis and HIV Disease," *BETA*, Winter 2002.)

HEPATITIS C COINFECTION

Studies presented at ICAAC shed further light on when to continue hepatitis C treatment—and for how long—in HIV/HCV-coinfected individuals. Juan Berenguer, MD, PhD, from Hospital General Universitario Gregorio Marañón in Madrid (abstract V-1726) reported that coinfected people who do not achieve an early virological response to standard interferon/ribavirin therapy (EVR, at least a 2 log decrease in HCV RNA by 12 weeks) are unlikely to later achieve a sustained virological response (SVR, undetectable HCV viral load six months after the end of therapy). Among the 48 participants (36%) in this study who experienced an EVR, half went on to achieve an SVR.

Vincent Soriano, MD, from the Instituto de Salud Carlos III in Madrid (abstract H-1718) reported similar results from a study using pegylated interferon/ribavirin. Here, too, 58% of 89 coinfected subjects experienced at least a 2 log drop in HCV RNA after 12 weeks of therapy, but just over half of these early responders went on to achieve an SVR after six months. About one-third relapsed after the completion of therapy, regardless of HCV genotype. In both studies, no subject who failed to achieve an early response by 12 weeks went on to achieve a sustained response with continued treatment. Both researchers concluded that it may be advisable to stop treatment in HIV/HCV-coinfected people after 12 weeks if no response is seen, as is recommended for HIV negative people with HCV. Dr. Soriano's results further suggest that coinfected people clear HCV more slowly than HIV negative individuals, and may therefore benefit from 18 months of therapy for HCV genotypes 1 or 4—which are harder to treat—and 12 months for genotypes 2 or 3. (The usual recommendation for HIV negative people is 12 months for HCV genotypes 1 or 4, and six months for genotypes 2 or 3.)

Shyam Kottilil, MD, of the NIH (abstract V-1724) and colleagues reported that although only one of 11 coinfected subjects treated with pegylated interferon/ribavirin achieved an SVR in their study, all treated individuals had improved biochemical markers of liver function, and all ten who had pre- and post-treatment liver biopsies showed improved histology (tissue damage) scores, even if they did not achieve a virological response. Dr. Kottilil suggested that the 12-week cutoff may be too soon for HIV/HCV-coinfected individuals, and that more people might achieve an SVR with longer treatment.

Carmen Quereda, MD, from Hospital Ramón y Cajal in Madrid (abstract V-778) reported that concomitant therapy for both HCV and HIV may lead to lower rates of response to HCV treatment. In this study, 27 coinfected participants who were not on anti-HIV therapy and 108 who were taking anti-HIV drugs started HCV treatment. Those who were not on anti-HIV therapy were more likely to achieve an end-of-treatment response (60% vs 33%) and an SVR (41% vs 19%) with interferon/ribavirin treatment. Among

those taking HAART, anti-HCV therapy was less well tolerated, and subjects in this group were twice as likely either to stop interferon or have their doses adjusted. On the other hand, Curtis Cooper, MD, from the University of Ottawa (abstract H-826) reported that among 236 coinfected subjects, liver fibrosis (scarring) appeared to progress more slowly in those receiving HAART compared with those not receiving anti-HIV treatment.

For HIV/HCV-coinfected people who do use anti-HIV therapy, Douglas Dieterich, MD, from Mt. Sinai School of Medicine in New York City (abstract H-831) reported that nelfinavir appears to be a safe and effective component of combination treatment for people with HCV, causing fewer severe (grade 3 or 4) liver enzyme elevations than other PIs (including amprenavir, indinavir, ritonavir, and saquinavir).

In related news, German researchers reported in the November 22, 2003 issue of *The Lancet* that HAART reduced the rate of death due to liver-related causes in HIV/HCV-coinfected individuals. Analyzing a cohort of 285 coinfected subjects observed between 1990 and 2002, the researchers found that liver-related mortality was lower in individuals treated with HAART (2 deaths out of 93 people, or 0.45 deaths per 100 patient-years) than in those treated with dual or monotherapy (5 out of 55, or 0.69 deaths per 100 patient-years) and those not receiving any antiretroviral therapy (18 out of 137, or 1.70 deaths per 100 patient-years). Notably, no participants in this study were using interferon for treatment of HCV. Severe drug-related liver toxicity was seen in 13.8% of those taking HAART. "In addition to improving overall survival, effective antiretroviral therapy also lowers mortality from HCV-associated chronic liver disease," the authors concluded. In an accompanying editorial in the same issue, Nadia Alatrakchi, MD, and Margaret James Koziel, MD, of Harvard Medical School wrote, "The risks of hepatotoxicity, although real, should not diminish the use of HAART."

SEX DIFFERENCES IN LIPODYSTROPHY

Two recent studies shed further light on sex differences in body fat changes in people with HIV, although their conflicting findings indicate that there is still much to be learned.

Massimo Galli, MD, and colleagues from the Lipodystrophy Italian Multicentre Study analyzed 2,258 subjects seen at six HIV treatment centers in Italy, including 673 (about 30%) women. Results were published in the September 1, 2003 issue of the *Journal of Acquired Immune Deficiency Syndromes*. In this study, more of the women were treatment-naive, more men had taken PIs, median HAART duration and frequency of d4T use (a drug often associated with peripheral fat loss) were similar, and men were more likely to have severe HIV disease. Adipose (fat) tissue alterations (self-reported and confirmed by physicians) were present in 282 women (41.9%) and 468 men (29.5%). Women were more likely to gain fat in any region of the body, including the breasts, and were more likely to have a mixed pattern of fat gain and loss. Absolute rates of pure fat loss in the limbs, buttocks, and face were similar in both sexes, although it was the most commonly reported alteration in men and the least frequently reported in women. Interestingly, women who had never taken antiretroviral therapy were more likely to report body fat changes than treatment-naive men (10% vs 7%, respectively). "Lipodystrophy is more frequent and more polymorphic in women than men," the authors concluded. "The results of this large cross-sectional study clearly show that women are at a higher risk of developing adipose tissue alterations than men." They suggested that hormonal mechanisms may play a role in these differences.

In the December 15, 2003 issue of *AIDS*, Phyllis Tien, MD, of UCSF and colleagues published results of an analysis of peripheral (arms, legs, and/or buttocks) and central (waist, chest, and/or upper back) fat loss (lipoatrophy) and fat gain (lipohypertrophy) in 815 women (605 HIV positive and 210 HIV negative) in WIHS, the Women's Interagency HIV Study. This study differed from most previous lipodystrophy research in that it used more rigorous definitions of fat changes, confirmed self-reported changes with anthropometric measurements, and included an HIV negative control group; the study did not analyze the effects of antiretroviral therapy. During the 30-month study period, weight and body fat percentage increased among the HIV negative women—as expected in middle-aged women—but remained stable in the HIV positive women. Overall, 49% of HIV positive women and 42% of HIV negative women experienced some type of body fat change. The HIV positive women had about twice the rate of both peripheral (27% vs 13%) and central (23% vs 13%) fat loss compared with the HIV negative women. The HIV positive women appeared less likely to gain peripheral fat (18% vs 25%), while central fat gain was about equal in both groups (28% vs 31%).

Many researchers have assumed that peripheral fat loss and central fat gain are complementary components of lipodystrophy syndrome. However, in this study, most women who experienced more than one type of body shape change developed either both peripheral and central fat loss, or both peripheral and central fat gain. A mixed pattern of peripheral lipoatrophy plus central lipohypertrophy was uncommon (occurring in 14% of the HIV positive and 4% of the HIV negative women), while mixed peripheral fat gain plus central fat loss was not reported. These findings suggest that "HIV-associated lipoatrophy syndrome affecting both peripheral and central sites may predominate in women," the authors concluded. "The presence of peripheral lipoatrophy in combination with central lipohypertrophy was uncommon in these women; therefore, lipoatrophy and lipohypertrophy should be assessed separately."

MOTHER-TO-CHILD HIV TRANSMISSION

Evidence continues to accumulate that antiretroviral therapy can dramatically reduce the risk of mother-to-child

(vertical) HIV transmission. It is well known that giving nevirapine or AZT to HIV positive women during pregnancy and/or delivery and to the infant after birth can prevent viral transmission. However, in resource-poor settings, women may arrive at a hospital just before giving birth and often do not know their HIV status, ruling out the recommended prenatal/intrapartum (during delivery) treatment strategy.

Now, a study reported in the October 11 issue of *The Lancet* indicates that giving nevirapine plus AZT to newborns can reduce transmission even if the mothers themselves were not treated. Taha El Tahir Taha, PhD, MPH, from Johns Hopkins and colleagues gave nevirapine with or without AZT to 1,119 infants born to HIV positive mothers in Malawi. All babies received a single dose of nevirapine immediately after birth; about half also received twice-daily AZT for one week. Infants were tested for HIV at birth and again after 6–8 weeks. Overall, 15.3% of babies in the AZT/nevirapine group and 20.9% in the nevirapine only group were infected. (Without treatment, the vertical transmission rate is about 25%.) Among infants not infected at birth, 7.7% who took AZT/nevirapine and 12.1% who took nevirapine alone seroconverted by 6–8 weeks—a risk reduction of 36%.

In developing countries, where infant formula and clean water may not be readily available, babies who are not infected at birth still often contract HIV through breast-feeding. At the IAS meeting, Joep Lange, MD, from the University of Amsterdam (abstract LB07) reported that treatment of infants with antiretroviral drugs may help prevent transmission via breast milk. In the SIMBA study, Dr. Lange and colleagues gave daily 3TC or nevirapine to 397 infants born to HIV positive mothers in Rwanda and Uganda from birth until a month after weaning. The mothers received AZT/ddI during pregnancy and delivery; they breast-fed their infants for a median of about 100 days (about 90% exclusively). Infants were tested for HIV six months after birth. Postnatal HIV transmission occurred in only 1.1% (2 out of 179) of the infants receiving 3TC and 0.6% (1 out of 179) of those receiving nevirapine. Without therapy, the rate of transmission via breast-feeding is about 15%. Said Dr. Lange, "With a relatively simple intervention you can prevent nearly all these children who were not infected [at birth] from becoming infected."

SMALLPOX VACCINE MAY DISCOURAGE HIV INFECTION

Results from a small study suggest that the smallpox vaccine may also protect against HIV infection, according to Kenneth Alibek, MD, PhD, and colleagues from George Mason University's National Center for Biodefense. Some have posited a connection since the rapid spread of HIV in Africa coincided with the elimination of smallpox and the cessation of routine vaccination in the 1980s. Researchers studied blood samples from ten people who received the smallpox vaccine and ten who did not. In laboratory studies, HIV did not replicate or did so at reduced levels when added to the samples from the vaccinated individuals. The researchers reported a four-fold reduction in viral infectivity. Coworkers from George Washington University emphasized that the results are speculative, and people at risk for HIV should not seek out smallpox vaccination. The vaccine is not recommended for people already infected with HIV.

HIV INFECTIONS CONTINUE TO RISE

Building upon data presented at the 2003 Conference on Retroviruses and Opportunistic Infections showing a rise in new HIV infections between 1999 and 2001, more recent figures indicate a continued increase in 2002. In the November 28, 2003 issue of *Morbidity and Mortality Weekly Report*, the CDC reported that between 1999 and 2002 new HIV diagnoses increased 17% among men who have sex with men. During this period a total of 102,590 new infections were reported. The analysis includes data from the 29 states with name-based HIV reporting, which omits some areas—including California, New York, and Washington, DC—with high HIV/AIDS prevalence. Among the new HIV cases, 70.5% were in men and 29.5% were in women. By ethnicity, infection rates remained highest among African Americans (55%), but increased by 26% among Latinos. According to Robert Janssen, MD, director of the CDC's Division of HIV/AIDS Prevention, HIV testing rates remained steady during the study period.

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TIPRANAVIR: *the First Nonpeptidic Protease Inhibitor*

Nicholas Cheonis

Resistance to anti-HIV medications is an ongoing dilemma. A recent study in 16 European countries and Israel found primary drug resistance mutations in 10% of 1,633 people newly diagnosed with HIV disease who had never taken anti-HIV therapy. French clinicians have reported that 78% of viral samples taken between 1997 and 2002 from over 2,000 chronically infected people showed some resistance to at least one antiretroviral drug, and 25% had some resistance to three major drug classes (excluding fusion inhibitors). Similar findings have been reported in the U.S. and Britain. As a significant number of people with HIV find themselves with fewer treatment options, researchers struggle to develop medications that remain effective against genetically varied forms of the virus.

Tipranavir, the first in a new category of protease inhibitors (PIs), appears to be such a drug. Studies have shown that tipranavir (formerly known as PNU-140690) durably reduces viral load in some people whose dominant HIV strain is resistant to at least two other PIs. The quality of tipranavir resistance that does develop has also been examined, and the extent of this agent's usefulness in people needing salvage therapy is under investigation.

Recent Data

Early *in vitro* (test-tube) studies of tipranavir were impressive. Brendan A. Larder, PhD, of Virco and colleagues reported in the September 8, 2000 edition of *AIDS* that 90% of 105 HIV isolates highly resistant (more than ten-fold) to approved PIs—in this case, indinavir (Crixivan), nelfinavir (Viracept), ritonavir (Norvir), and saquinavir (Fortovase)—were highly sensitive to tipranavir. Only 2% were highly resistant to the experimental PI; the remaining 8% had moderate (four- to ten-fold) resistance.

This was an important finding, since the virological benefit of PIs (i.e., reduced viral load) is blunted by high levels of cross-resistance, as seen in these viral isolates. (Viral isolates refer to HIV taken from infected individuals. Cross-resistance refers to genetic mutations in HIV that render some or all agents in the same drug class less effective.) The challenge was to reproduce such robust activity in human clinical studies.

BI 1182.2

Eighty-week data from a Phase II, randomized, open-label trial known as BI 1182.2 were reported this past October at the 9th European AIDS Conference in Warsaw. This study enrolled 41 subjects with unsuppressed viral load despite having used two or more PI-based regimens. None of the participants had used a non-nucleoside reverse transcriptase inhibitor (NNRTI). Median baseline viral load was 4.43 log (about 26,000) copies/mL and median baseline CD4 cell count was 273 cells/mm^3. Subjects were randomized to take either 1,200 mg of tipranavir plus 100 mg of ritonavir twice daily, or 2,400 mg of tipranavir plus 200 mg of ritonavir twice daily. All subjects also received 600 mg once daily of the NNRTI efavirenz (Sustiva) and two nucleoside reverse transcriptase inhibitors (NRTIs).

A soft-gel formulation of tipranavir, known as SEDDS, was introduced during the study. A majority of participants subsequently switched from the original "hard-filled" tipranavir capsules to the SEDDS version by week 48 at doses of 500 mg and 1,000 mg, respectively, along with 100 mg of ritonavir, all twice daily. Soft-gel SEDDS used with low-dose ritonavir reduced overall pill burden and greatly enhanced tipranavir bioavailability (the degree to which it is absorbed and circulated in the body).

At 80 weeks, the median viral load reduction was 2.55 log copies/mL (greater than 99%) for those taking the lower dose of tipranavir and similar (2.43 log) for those in the high-dose arm. In an as-treated analysis (which is less rigorous and clinically useful than an intent-to-treat analysis), the study authors noted that 43% in the low-dose arm and 90% in the high-dose arm had viral loads below 50 copies/mL at week 80. Using a test unable to measure below 400 copies/mL, 64% in the low-dose group and 90% taking the higher dose had undetectable viral loads. The median CD4 cell count increases were 175 cells/mm^3 and 143 cells/mm^3, respectively.

The most common adverse events reported in the low-dose arm were nausea (31%), diarrhea (26%), and increased levels of GGT (a bile duct enzyme; 26%) and triglycerides (a type of blood fat; 21%). In the high-dose arm, common side effects were diarrhea (72%), nausea (31%), increased levels of ALT (a liver enzyme; 27%), and vomiting (22%).

Encouragingly, this study showed a sustained virological response in some subjects with viral resistance to multiple PIs. Yet the original tipranavir formulation used during the beginning of the trial almost certainly affected some of the data and drop-out rates, particularly in the high-dose group, which had tolerability problems using the hard-filled capsules. Only 50% of subjects in the high-dose arm (compared with 74% in the low-dose arm) continued to week 80.

BI 1182.52

BI 1182.52 was a larger randomized, double-blind, international, Phase IIb trial designed to find the optimal dose of tipranavir/ritonavir for use in Phase III studies. Three tipranavir/ritonavir doses were given: 500/100 mg, 500/200 mg, and 750/200 mg, all twice daily. The 216 randomized subjects (15% female, 22% black) were followed for at least 24 weeks. All had used three classes of anti-HIV agents, and had detectable virus despite having used at least two PI-based regimens (excluding the most recently approved PIs, fosamprenavir [Lexiva] and atazanavir [Reyataz]). Median viral load was 4.5 log (about 32,000) copies/mL, and median CD4 cell count was 177 cells/mm^3.

At 24 weeks, 23 subjects (31%) in the 500/100 mg arm, 29 (40%) in the 500/200 mg arm, and 32 (45%) in the 750/200 mg arm had at least a 1 log (90%) decrease in viral load. The study authors found no statistical difference across the three arms. CD4 cell counts increased by an average of 10 cells/mm^3 in the 500/100 mg arm, 18 cells/mm^3 in the 500/200 mg arm, and 46 cells/mm^3 in the 750/200 mg arm. These figures were based on an intent-to-treat analysis, which included data on all subjects according to the original randomization.

Diarrhea and nausea were common in all study arms (an overall incidence of about 31%). Grade 3 (severe) or 4 (life-threatening) laboratory abnormalities were also noted in all arms, with the lowest incidence seen in subjects taking 500/100 mg. Among those taking 500/200 mg and 750/200 mg, the following increases were reported: AST (a liver enzyme) in 6.9% and 7.0%, ALT in 11.1% and 21.1%, bilirubin (a byproduct of red blood cell destruction) in 0% and 2.8%, cholesterol in 2.8% and 5.6%, and triglycerides in 27% and 22%, respectively.

The study authors concluded that tipranavir-based therapy was effective in the 500/200 mg and 750/200 mg arms, and that an acceptable safety profile was observed in the 500/100 mg and 500/200 mg arms. As a result, tipranavir is currently being studied at the 500 mg dose with 200 mg of ritonavir twice daily (see "RESIST," below). Again, the ability of this experimental PI to suppress HIV in some heavily pretreated individuals has spurred continued research by the drug's developer, Boehringer Ingelheim.

Resistance Profile

Tipranavir has a unique structure: it is a nonpeptidic—and therefore more flexible—molecule, which may account for its increased potency. All currently available PIs are derived from peptides (short chains of amino acids; peptides combine to form proteins). Peptide-based PIs theoretically are less able to adapt their shape and disable HIV protease with minor structural changes, a hallmark of mutated virus. The studies described above show that resistance to tipranavir does develop, although it appears to require a higher threshold of accumulated resistance mutations compared with other PIs.

Resistance mutations are detected using a genotypic test. Mutations are normally referred to by numbers, such as 10 or 36, that indicate their position on a particular HIV gene. Broad cross-resistance to PIs is often seen in HIV with mutations at positions 33, 82, 84, and 90 of the protease gene; these are known as universal protease inhibitor-associated mutations, or UPAMs. Mutations are also divided into primary and secondary categories. Anti-HIV drugs are each associated with at least one primary mutation that is a strong predictor of drug resistance. Secondary mutations may render HIV less sensitive to a specific drug, but do not normally lead to high-level resistance in the absence of a primary mutation. The risk of PI resistance increases as more mutations to the protease gene accumulate.

Researchers found a low rate of resistance to tipranavir in study BI 1182.2. High-level resistance to the drug was seen in only one (2%) and decreased susceptibility in only six (14%) of the 41 subjects, all of whom had detectable virus when using other PIs. Decreased susceptibility—which does not necessarily imply reduced virological response—was associated with an average of 16 mutations including two or three UPAMs. Notably, the number of baseline protease gene mutations did not predict reduction in viral load.

Resistance data from the larger BI 1182.52 study have also shown that susceptibility to tipranavir is maintained despite multiple protease mutations. In separate analyses, it appeared that at least three baseline UPAMs, and 16 to 20 total mutations, were required to impair virological response to the drug. In contrast, similarly reduced susceptibility to other PIs may be associated with only one or two UPAMs. (For more information on drug resistance, see "Genotypic and Phenotypic Resistance Testing," *BETA*, Summer 1999.)

Drug Interactions

Interactions between tipranavir and other agents have been reported. Tipranavir can lower blood levels of the

NNRTI delavirdine (Rescriptor) by 95%, so the two drugs should not be used together. The antibiotic rifampicin (Rifadin, Rimactane) is also contraindicated. Enteric-coated ddI (didanosine, Videx EC) should be taken four hours before or after tipranavir. Blood levels of AZT (zidovudine, Retrovir) are reduced by 33–43% in the presence of tipranavir, though standard AZT doses are believed to be adequate. In addition, antacids reduce tipranavir blood levels by 30%.

RESIST

A set of Phase III studies known as RESIST (Randomized Evaluation of Strategic Intervention in Multidrug Resistant Patients with Tipranavir) is currently underway. The RESIST 1 and 2 trials will study tipranavir in subjects who have used NRTIs, NNRTIs, and PIs, and have limited treatment options. These randomized, open-label studies will compare the safety and efficacy of 500/200 mg tipranavir/ritonavir against another ritonavir-boosted PI, which will be selected according to resistance testing and treatment history.

RESIST 1 recently completed enrollment of 500 participants in North America and Australia, while RESIST 2 aims to enroll at least 800 participants in Europe and South America. Some study sites are running companion trials (RESIST 3 and study 1182.51) for people with extensive treatment experience who do not qualify for the larger RESIST 1 or 2 studies.

RESIST should further reveal the utility of tipranavir and its side effect profile in a larger pool of individuals with antiretroviral resistance. Nevertheless, for people with more than two UPAMs, careful selection of drugs will remain essential.

Nicholas Cheonis is editor of *BETA*.

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Schwartz, R. and others. Resistance to tipranavir is uncommon in a randomized trial of tipranavir/ritonavir (TPV/RTV) in multiple PI-failure patients (BI 1182.2.). 9th CROI. Seattle. February 24–28, 2002. Abstract 562-T.

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Wensing, A.M.J. and others. Analysis from more than 1,600 newly diagnosed patients with HIV from 17 European countries shows that 10% of the patients carry primary drug resistance: the CATCH-study. 2nd IAS Conference. Abstract LB1.

See page 46 for information on a trial of TMC114, a PI in Phase II development that also may be effective against PI-resistant HIV.

Overcoming Depression

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George Harrison, MD

Depression is one of the most prevalent and undertreated complications of HIV disease. Despite the improvements in health related to highly active antiretroviral therapy (HAART), women and men with HIV continue to be at risk for depression. Untreated depression not only can affect quality of life, but it also may compromise HAART adherence, weaken immune functioning, exacerbate chronic pain, and contribute to substance use. Depression might also lead to increased sexual risk-taking behavior in some people with HIV, potentially contributing to HIV transmission.

This article will address a range of questions concerning HIV-related depression. Why is depression so common in people with HIV? Is it seen more frequently in those with HIV disease than in uninfected individuals? If so, why? And if depression is so common, why is it typically overlooked by HIV clinicians? Finally, is depression treated differently in people with HIV, and what specific types of therapy or medications are most useful?

What Is Depression?

Like many disorders, depression is a syndrome, meaning it is characterized by a set of symptoms. A chief feature may be expressions of mood such as sadness or worry. These will often be accompanied by cognitive (related to perception, learning, and reasoning) symptoms such as poor concentration or complaints of memory loss. Often there are also physical signals including changes in sleep, appetite, libido (sexual desire), pain tolerance, or energy (see sidebar on page 21).

Importantly, the many presentations of depression are diverse, and the constellation of symptoms overlaps many other mental, behavioral, and physical disorders. For example, a depression diagnosis might be missed if the individual does not look sad but rather appears irritable, anxious, or excessively worried. Alternately, depressive symptoms may be caused by a coexisting medical condition such as fatigue associated with HIV, hepatitis C, or hypothyroidism (low thyroid hormone production).

The exact causes of depression are not known. Practically speaking, depression is associated with the faulty activity of brain hormones (neurotransmitters). Endogenous (produced by and for the brain) neurotransmitters such as serotonin, norepinephrine, and dopamine are necessary for normal brain and body function. When neurotransmitters are less active or lacking, dysfunction of brain and body processes follows. Why this disregulation of brain hormones occurs is far from understood. However, the effects of impaired neurotransmitter activity are well recognized: they cause a diverse set of changes in mood, thinking, energy, pain perception, and physical well-being.

The various effects of neurotransmitters are typical of substances that act on the brain. Caffeine, for example, can affect mood (it has antidepressant properties and can cause irritability), alertness, heart rhythm, and sleep. Likewise, nicotine, which also has receptors in the brain, can modulate mood, cognition, and energy.

Risk Factors

While the specific causes of depression are not established, many factors are known to increase the risk of this disorder (see sidebar on this page). One important—and unmodifiable—risk factor is family history. The risk of having a depressive disorder is increased if a family member has a mood disorder. The genetic mechanisms behind this heritability (is it due to one gene, or several? is it dependent on life experiences for expression?) are under investigation. Relatives may not have a diagnosis of depression per se, yet may show signs of suffering from debilitating depression: suicide attempts, "nervous breakdowns," unexplained functioning problems, or self-medication with substances such as alcohol or drugs.

RISK FACTORS FOR DEPRESSION

- family history of depression
- family history of substance use
- history of childhood or adult trauma
- history of prior or current substance use
- diagnosis of brain disorder (e.g., HIV-related dementia, head trauma, stroke)
- history of multiple or cumulative stressors

CONDITIONS THAT CAN MIMIC DEPRESSION

- hypogonadism (low testosterone)
- hypothyroidism (low thyroid hormone)
- advanced (tertiary) syphilis
- substance use
- vitamin B_{12} deficiency
- advanced liver disease

Another important risk factor for adult depression is trauma or neglect during childhood. Epidemiological studies of humans, and experiments with primates, have shown that chaotic conditions or a lack of nurturing during childhood predispose individuals to depression as adults. For example, infant monkeys who are removed from their mothers for several months are more susceptible to depression when stressed as adults.

Adult trauma (violence, rape, severe loss) also increases the risk of depression. Significantly, coping with a diagnosis of a life-threatening disease such as HIV may be traumatizing. For some people, being diagnosed with HIV can be terrifying and result in the loss of relationships and the disruption of life plans. Several identifiable crescendo points of stress are associated with HIV illness, including a new HIV diagnosis, a first significant HIV-related illness, and a drastically reduced functional level if HIV disease progresses. Many people with HIV live in marginal circumstances and are already trying to cope with poverty or violence. For these individuals an HIV diagnosis may have an additive stressful effect.

One-third of people who have a substance use or dependence disorder also suffer from depression. A syndrome of acute mood changes associated with drug intoxication and withdrawal is well described. For example, stimulant (e.g., speed, cocaine) use can lead to depressive symptoms.

Ironically, self-medicating with substances such as alcohol, speed, or heroin may be an attempt to treat depressive symptoms such as fatigue or listlessness. While these substances may temporarily mask depressive symptoms, they exacerbate depression over time. Long-term exposure to these substances may cause a direct effect on brain chemistry that appears to be associated with depression or other serious mental illness. Substance dependence may also cause disruption of social functioning (e.g., relationship or workplace problems), which puts the individual at further risk for a mood disorder.

Prevalence of Depression in HIV Disease

An important, and unresolved, question is whether depression is more common in HIV positive people than in the HIV negative population. This basic question is surprisingly difficult to answer. First, depression is more difficult to diagnose accurately in people with medical conditions such as HIV. An HIV positive person with fatigue, low sex drive, and cognitive problems could be experiencing depression, or these symptoms could be due to HIV itself. Second, people with HIV and depression may be depressed not because of their HIV infection, but because of other associated conditions such as substance use.

However, depression is at least as prevalent in HIV positive people as in those who are HIV negative. Depression is very common in the general population, affecting 5–15% of people at any given time, with a lifetime risk ranging between 15% and 25%, depending on survey methods. Women are about twice as likely as men to experience depression. Some studies show that there is an increased rate of depression in people who are HIV positive compared with the general population. Yet after controlling for confounding factors such as substance use or demographic information such as sexual orientation, the differences in rates are less clear. (The prevalence of depression may be increased in lesbians and gay men, perhaps as a result of isolation or coping with homophobia.) Experts note that most HIV positive people with depression have risk factors aside from HIV infection.

Depending on how depression is defined and on the population being studied (women vs men, substance users vs nonusers, teens vs adults), the prevalence of depression in studies of people with HIV has ranged from 10% to 50%. Even if the lowest estimates are accurate, depression remains one of the most common conditions seen in people with HIV. Yet depression is a diagnosable and frequently treatable illness. The first step is recognizing the condition.

Screening for Depression

Standardized screening tests for depression include questionnaires conducted by clinicians, as well as those that individuals can take on their own. These questionnaires are screening tools; while they do not prove that someone is depressed, they seldom result in false negatives (i.e., miss depression). When recommending or using these exams, it is important to remember that they have been validated in the general population, but have not been specifically normalized for an HIV positive population.

Three common clinician-administered screening tools are the Zung Self-Rating Depression Scale, the Hamilton Depression Scale, and the Beck Depression Inventory. These can be accessed online at **www.fpnotebook.com/psych8.htm.** In addition, several web sites offer self-administered tests (see sidebar on this page).

As an example of these tools, the Hamilton Depression Scale is a standardized depression screen used by clinicians and researchers. By assigning a gradated set of points to various symptoms, clinicians can both diagnose depression and assess its severity. Most depression studies use this or other scales to gauge the efficacy of interventions, as well as to characterize the population being studied. In effect, the Hamilton rating score is analogous to CD4 cell counts in HIV disease.

A streamlined and reasonably reliable depression screen is the following two-question survey that focuses on depressed mood and one other symptom, anhedonia (lack of pleasure): *1) Are you sad or depressed frequently? 2) Are you unable to enjoy activities you normally find enjoyable?* If the answer to both questions is no, there is less than a 5% probability of depression.

Diagnosing Depression

Diagnosing depression is challenging in any population with chronic, coexisting conditions. As mentioned above, coexisting, or "comorbid," conditions may cause physical symptoms that mimic the

DEPRESSION SCREENING TEST SITES

National Mental Health Association (NMHA)
www.depression-screening.org/screeningtest/screeningtest.htm

New York University Department of Psychiatry
www.med.nyu.edu/Psych/screens/depres.html

University of Michigan Department of Psychiatry
www.med.umich.edu/depression/screen.htm

symptoms of depression. Likewise, distinguishing between abnormal mood due to depression versus normal mood fluctuations caused by the stress of a chronic medical illness may be difficult. This overlap of physical and emotional symptoms often results in the underdiagnosis of depression. Clinicians may mistakenly attribute symptoms of depression to HIV itself or to medication side effects (fatigue, poor sleep, concentration problems). They may also attribute depressive mood symptoms (flat mood, irritability) to a normal reaction to living with HIV.

Clinicians' missing the physical and mood clues of depression has been documented in cancer and geriatric (elderly) populations as well as in people with HIV. Given that the physical symptoms of HIV disease and depression may be identical, and that a gray line exists between depressive mood symptoms and a normal reaction to stressors (referred to formally as an "adjustment disorder"), how can depression be accurately diagnosed in people with HIV?

A few practical principles can address these diagnostic challenges:

- depression is common
- the presence of risk factors for depression reliably increases diagnostic accuracy (see Risk Factors sidebar on page 19)
- several medical conditions can mimic depression and should be excluded in all HIV positive people with suspected depression (see sidebar on page 19)
- all studied antidepressants have equal efficacy in HIV positive and HIV negative individuals
- given the impact of untreated depression, a trial of psychotherapy, antidepressants, or both should be offered in uncertain cases

This last principle is considered an "inclusive" approach to depression diagnosis. In this approach, all symptoms that may be associated with either depression or HIV are assumed to be due to depression. While this approach may overdiagnose depression, it prevents the underdiagnosis of the condition, which is far more likely in general.

Treatment for Depression

Treatment for depression includes counseling (psychotherapy), lifestyle changes, and medications. While these interventions will be discussed separately, they are complementary and often work best when used in combination. In some instances, treatments have been studied specifically in people with HIV, as noted below. In most cases, however, interventions have been formally studied in the general population but their usefulness in people with HIV has been confirmed by anecdotal experience.

Counseling

A large variety of group and individual counseling approaches have been used (and some of them studied) in HIV positive people suffering from depression. Because of the social, psychological, and neuropsychiatric consequences of HIV/AIDS, an individual might benefit from interventions spanning a spectrum from individual to family or group psychotherapy as well as psychodynamic/psychoanalytic, interpersonal, behavioral, and supportive approaches. Group work—from supervised group counseling to less formal peer support groups—can be especially useful for people with HIV who are isolated from other people with HIV infection. Individual therapy can be provided by therapists from a wide range of disciplines: social workers, marriage and family counselors, psychologists, and psychiatrists. For good referral sources, see sidebar on page 23.

Several principles hold across the variety of psychotherapy styles. The therapist should be familiar with HIV disease and understand the basics of HIV treatment. Substance use should be addressed, and if appropriate, referral to substance abuse resources given. In addition, the therapist should help the client explore and develop effective coping mechanisms; this may include dealing with HIV disclosure to family, partners, and employers, or addressing spiritual issues.

After undergoing a mental health assessment, the individual can be presented with the range of possible counseling methods. Identifying a specific type of therapy to use, and locating available resources, is not always easy. Referral outcomes may be improved if the individual has an

SYMPTOMS OF DEPRESSION

Physical

- sleep disorders
  - difficulty falling asleep
  - disrupted sleep
  - early awakening
  - excessive sleeping
- fatigue, especially on waking
- low sex drive
- impaired concentration
- unexplained pain, especially abdominal pain or headache
- decreased or increased appetite

Mood

- irritability
- worry/rumination
- sadness/weepiness
- anhedonia, or inability to enjoy activities
- lack of motivation
- hopelessness
- self-blame/guilt
- lowered self-esteem
- suicidal ideation, or thoughts of committing suicide

accurate idea of what the treatment will be like. For the individual seeking therapy, preparing for the structure and expectations of counseling will decrease anxiety and make the process more engaging and dynamic.

For providers, a challenge of working in a large urban environment may be keeping track of the various counseling options available in the community. In areas without large numbers of HIV positive people, clinicians should be familiar with providers in the community who are skilled in working with different populations.

For HIV positive individuals, undertaking depression treatment is a complicated task, particularly when it involves counseling. Consultation and teamwork are the cornerstones of effective treatment due to the convergence of many different areas of clinical focus. It is likely that no single clinician will have an adequate depth of knowledge about all the medical, social, mental health, and/or substance use issues that will need to be addressed. Good communication between different providers—including social workers, therapists, substance use counselors, and primary care physicians—will help to enhance the effectiveness of any intervention.

Lifestyle Changes

While depression clearly disrupts daily living, it is easy to overlook the impact that lifestyle changes can have on this condition. Altering basic activities, including sleeping, eating, socializing, and exercise, can be a very effective intervention.

Sleep is often disordered in people with depression, who tend to get either too little sleep or excessive amounts. The principles of optimized sleep (known as sleep hygiene) include having regular waking and sleeping times, decreasing dependence on naps, reducing the use of stimulants such as caffeine, and making the sleep environment as conducive to sleep as possible. These seemingly simple guidelines are often more difficult to follow than they would appear. However, the benefits may be substantial, and are not replicated by use of sleeping medication.

Nutrition, which is often a focus of attention in HIV positive people, may also be disordered (resulting from overeating or loss of appetite) in those with depression. Proper nutrition has obvious health benefits. It might also provide a less appreciated sense of well-being. The rhythm of regular meals can serve as a structuring element in a person's day to which other activities may be added. Including a social component with eating may further improve mental health.

Isolation contributes to depression and is a significant issue for some people with HIV. For many depressed people, increasing social contact is an important factor in their improvement. Isolation may be reduced by involvement in volunteer work, group activities based on common social or spiritual interests, structured day treatment settings, or having a pet.

While pet ownership for people with HIV has not been formally studied, pet stewardship has been analyzed in the general population and in the elderly, and has been shown to correlate with improved quality-of-life and disease-specific outcomes. Exactly how pets may enhance health is not known. The benefits may derive from a sense of structure (e.g., walking the dog), feelings of being needed, physical contact, and increased interactions with other pet owners. While having a pet does entail daily responsibilities and expense, for some people these costs are worthwhile.

Exercise may help reduce depressive symptoms as well as potentially improve muscle and immune function, sleep, and stamina. Exercise can be an enjoyable part of life, but many people—even without depression—are disinclined to take regular physical exercise. Exercise programs should be designed to fit each person's goals and limitations, and must be modified over time.

While living well would appear to be sensible, few of us are good at accomplishing these basic tasks as well as we could. When there are intervening HIV complications and depression, these life-enhancing tasks can become additional stressors. Often there is little motivation to make lifestyle changes. Clinicians should provide support and guidance to help individuals overcome barriers to using these important tools for the resolution of depression. Success in accomplishing some of these goals will also give the individual a sense of control that may be lacking.

Medications

Antidepressant medications work by increasing the availability of neurotransmitters in the brain, or central nervous system (CNS). Just as antiretroviral drugs are categorized in classes such as protease inhibitors (PIs), antidepressants can be classed according to which hormone or hormones they act upon, and by what mechanism.

The two main concerns about antidepressants and people with HIV disease—whether the drugs work and whether they are safe—have been addressed and resolved. All antidepressants that have been studied in HIV positive people have shown efficacy comparable to their results in HIV negative individuals. Safety issues have centered on drug interactions between antidepressants and antiretrovirals. As discussed below, most of these interactions are not clinically significant, and aside from the interactions mentioned, standard doses of antidepressants are appropriate for people on anti-HIV therapy.

There are several types of antidepressant agents. Selective serotonin reuptake inhibitors, or SSRIs, are the most commonly used in people who have both depression and anxiety problems. These include fluoxetine (Prozac), sertraline (Zoloft), and escitalopram (Lexapro). Drugs such as imipramine (Tofranil), amitriptyline (Elavil), and nortriptyline (Pamelor)

REFERRAL SOURCES FOR COUNSELING

SAN FRANCISCO

- AIDS Health Project: 415-476-3902
- Asian and Pacific Islander Wellness Center: 415-292-3400
- Center for Special Problems: 415-292-1500
- Instituto Familiar de la Raza: 415-647-5450
- Iris Center: 415-864-2364
- New Leaf: 415-626-7000

NATIONAL/INTERNATIONAL

- In New York City, visit **www.aidsnyc.org/links/counsel.html** for a listing of mental health service providers.
- Local AIDS service organizations (ASOs) may be able to provide referrals. A list of ASOs in the U.S. as well as links to international organizations can be found at **www.thebody.com/hotlines/other.html.**
- One of the best resources for referrals are primary medical clinics specializing in HIV care. Clinicians at these agencies should know the local resources and be able to refer people to appropriate services.

are known as tricyclic antidepressants, or TCAs. TCAs can be especially useful in depressed individuals with sleep or pain problems. Other medications include bupropion (Wellbutrin), which is also used for smoking cessation, and nefazodone (Serzone). Antidepressant agents known as monoamine oxidase inhibitors (MAOIs) are not widely used due to the risk of life-threatening hypertension (high blood pressure) and the potential for lethal drug interactions. (For a listing of antidepressant drugs, see chart on page 24.)

All antidepressants take 3–6 weeks to achieve their optimum effect. In general, side effects are most common within the first two weeks of therapy and often improve over time. Side effects are predicted based on drug category. By far the most publicized is sexual dysfunction associated with SSRIs. Sexual dysfunction can take the form of decreased libido, decreased arousability, or delayed orgasm. These symptoms occur in about 40% of people taking SSRIs and may be minimal or significant. SSRI-induced sexual dysfunction can be addressed with dosage reduction or use of other medications, such as bupropion.

Just as antiretroviral therapy must be individualized to suit each person with HIV, so too must antidepressant therapy. What might be a problematic side effect for one person might be a useful side effect for another. For example, an appetite promoter such as mirtazapine (Remeron) is generally avoided in obese people but may be an excellent choice for someone with impaired appetite or weight loss. The rule of thumb is to match potential side effects with the individual's symptoms. Extra caution should be used in treating people with prior central nervous system disease and advanced HIV.

Starting with a low antidepressant dose and escalating it cautiously over time to a normal dose is advised. A dosing strategy that complements an existing antiretroviral dosing schedule can increase medication adherence. Follow-up about missed doses can also identify barriers to adherence and improve results. Medisets (plastic pill boxes labeled by days of the week) can be a useful tool to stay organized and also to help identify which antidepressant doses are most frequently missed.

The absence of an antidepressant's effect does not rule out depression. While a majority of people with depression will notice improved functioning with their first trial of an antidepressant, treatment-resistant depression is well documented.

Drug interactions

Most antidepressants are metabolized by the same cytochrome P450 liver enzymes as PIs and nonnucleoside reverse transcriptase inhibitors (NNRTIs). Clinically important drug interactions (significant increases or decreases in drug levels) might therefore be expected between most HAART drugs and most antidepressants. Experience has taught clinicians differently, however; with a few important exceptions mentioned in the sidebar on page 25, antidepressant choice and dosage are not affected by antiretroviral therapy.

Standard doses of citalopram, mirtazapine, and bupropion appear to be relatively free of unexpected changes in serum levels of either the antidepressants or antiretrovirals. Bupropion is an example of an antidepressant for which an interaction with an antiretroviral (in this case, ritonavir [Norvir]) was initially and incorrectly assumed.

Some people take a variety of alternative, over-the-counter medications such as St. John's wort (*Hypericum perforatum*), S-adenosylmethionine (SAM-e), or melatonin. Very little is known to date about the interaction of these agents with antiretroviral drugs. One report has found that St. John's wort reduces levels of indinavir (Crixivan), and the U.S. Food and Drug Administration (FDA) has warned about use of this agent with PIs and NNRTIs. Data in HIV

Antidepressants

	MECHANISM	BENEFITS	DRAWBACKS
Selective Serotonin Reuptake Inhibitors (SSRIs): fluoxetine (Prozac) sertraline (Zoloft) paroxetine (Paxil) citalopram (Celexa) escitalopram (Lexapro)	raise serotonin levels (some with minor norepinephrine effect)	good for anxiety, post-traumatic stress disorder (PTSD)	sexual dysfunction in up to 40%, only fluoxetine and paroxetine available generically
Tricyclic Antidepressants (TCAs): imipramine (Tofranil) amitriptyline (Elavil) desipramine (Norpramin, Pertofrane) nortriptyline (Pamelor)	raise serotonin and norepinephrine levels	inexpensive, can promote sleep, may downregulate pain	overdose danger, sedation, dry mouth, dizziness, constipation, difficulty with urination, heart rhythm abnormalities
Atypical Antidepressants: bupropion (Wellbutrin)	raises dopamine and norepinephrine levels	energizing, little sexual dysfunction, now available in once-a-day formulation, aids smoking cessation	may aggravate anxiety, generic formulation taken three times daily
mirtazapine (Remeron)	raises serotonin and norepinephrine levels	generic available, increased appetite, sedation, little sexual dysfunction	weight gain, sedation
nefazodone (Serzone)	raises serotonin levels	promotes sleep, little sexual dysfunction	morning sedation, rare hepatotoxicity, infrequent stimulating effect
venlafaxine (Effexor)	raises levels of serotonin at low doses, and both serotonin and norepinephrine at moderate doses	stimulating	nongeneric, may be too excitatory, sexual dysfunction, higher doses moderately increase blood pressure

DRUG INTERACTIONS

ANTIDEPRESSANTS AND HAART

nefazodone (Serzone)
used with
ritonavir (Norvir), lopinavir/ritonavir (Kaletra), delavirdine (Rescriptor)

• expect to use lower than normal doses of nefazodone, follow for unexpected increase in side effects from the antidepressant or the antiretrovirals

tricyclic antidepressants (TCAs)
used with
ritonavir, lopinavir

• use lower than normal doses of the TCA, obtain serum levels of the TCA, check EKG for conduction delays

venlafaxine (Effexor)
used with
indinavir (Crixivan)

• venlafaxine may reduce the level of indinavir, consider an alternate antidepressant

St. John's wort (*Hypericum perforatum*)
used with
PIs or NNRTIs

• not recommended in combination

negative people have shown that St. John's wort has mild antidepressant effects.

Drug interactions may be more likely in people with hepatic (liver) impairment, the elderly, or those taking newer HAART combinations. Again, clinical experience to date has shown that dose modification of most antidepressants is not appropriate or necessary with most antiretrovirals.

Summary

With improved antiretroviral therapies, HIV disease has become a potentially manageable chronic condition. Like many chronic conditions, however, HIV disease is often accompanied by other illnesses. Effective diagnosis and treatment of comorbid conditions such as depression may be crucial to the success of HAART regimens and their potential to enhance quality of life.

Addressing depression is therefore an important task for people with HIV and their health-care providers. Depression is the most underdiagnosed and undertreated condition among people with HIV as well as in the general population. As both effective counseling and medication resources are available, it is critical that these therapies be utilized by HIV positive women and men who might benefit from them.

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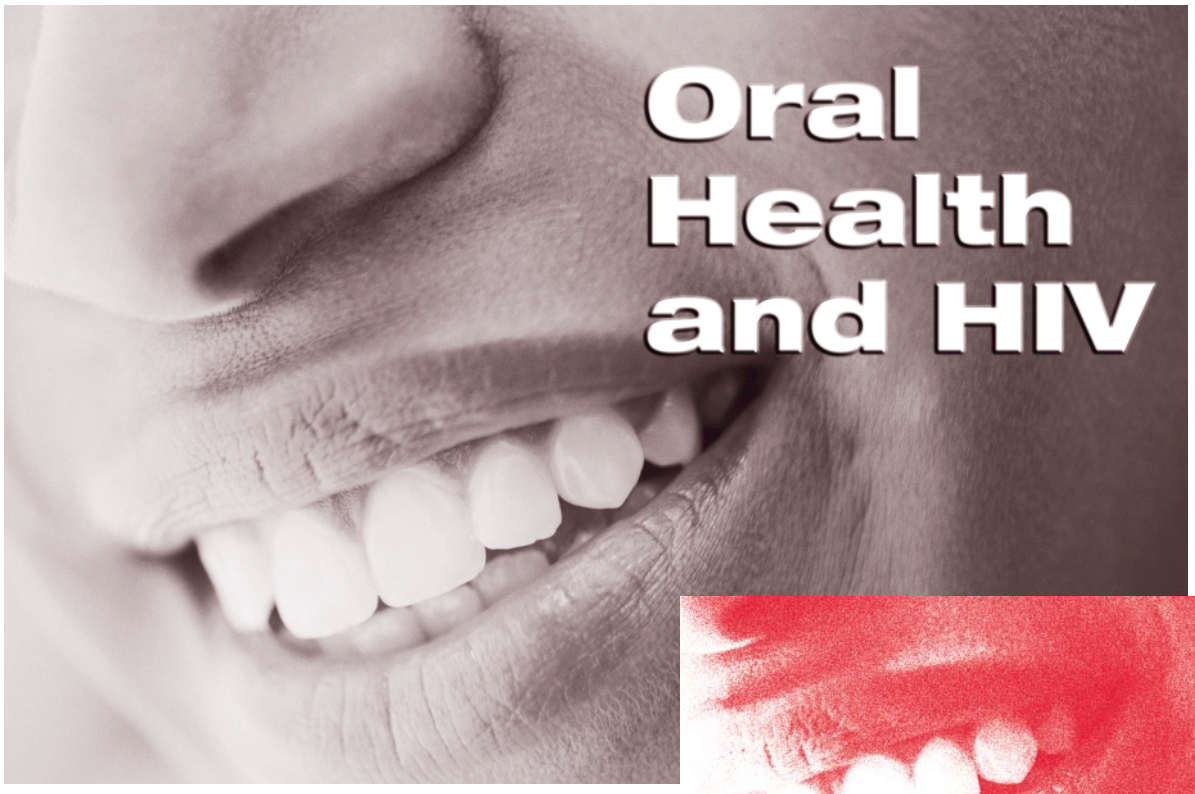
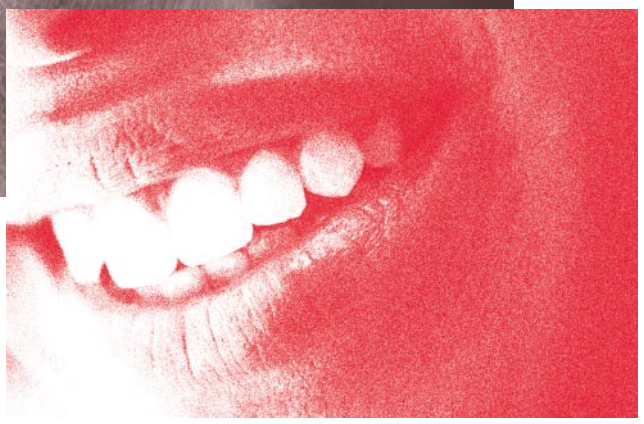


Oral Health and HIV

David I. Rosenstein, DMD, MPH



Most oral health problems can be found in people who are either HIV positive or negative. Yet there are some important differences. A few conditions are seen almost exclusively in people with HIV, while some that are found in both populations are more problematic for people with HIV, especially those with advanced disease. A diminished immune system can alter the course of oral disease and require more aggressive treatment to prevent minor troubles from escalating into major health problems.

Over 30 different oral manifestations of HIV disease have been reported since the beginning of the AIDS epidemic. This article will address several of the most common of these oral health issues. As with any health condition faced by HIV positive people, early identification and treatment should be emphasized. In many cases, referral to a dentist should be made as soon as possible.

Oral Health and People with HIV

The teeth are fully formed by the teenage years, and are not affected directly by HIV or anti-HIV medications. Reduced bone mineral density seen in people with HIV does not affect tooth enamel (the hard surface of exposed teeth), and it is unknown what affect, if any, it may have on the underlying bone that supports the teeth.

No treatment of any oral health problem should be avoided simply because a person is HIV positive. Reports early in the AIDS epidemic suggested that procedures such as root canals should not be performed in people with HIV. There were also suggestions that dental treatment should be postponed for anyone with a CD4 cell count below 200 cells/mm^3. Though these reports were inaccurate, their impact continues to be felt; some textbooks with recent publication dates still contain these misstatements. Dentists who follow these erroneous recommendations do so in violation of the Americans with Disabilities Act, and in violation of accepted community standards.

All procedures and devices—including periodontal surgery, endodontics (root canals), orthodontics (braces and retainers), implants, bleaching, and bridges—can be safely and effectively provided regardless of immune status. Decisions about such procedures should be made by the HIV positive individual in consultation with his or her dentist. As always, one should weigh the cost and time of the service against the expected benefits.

Common Oral Conditions

While dentists recommend that all people seek routine care to prevent oral health problems from developing, this is particularly important for those living with HIV. One rationale for this preventive measure is that individuals with a compromised immune system need to avoid bacterial infections. The two major oral health conditions, dental caries and periodontal disease, are both caused by bacteria and may be exacerbated by other factors.

Caries and Dry Mouth

Dental decay, or caries, is a common problem in the general population, and having a few carious lesions (cavities) is not unusual. These are typically prevented by the use of fluoride and good oral hygiene, including regular brushing and flossing of the teeth and gums.

Some medications used by people with HIV—and even HIV itself—may cause decreased salivary flow, or dry mouth, which is known to contribute to rampant caries. These lesions frequently develop at the cervical region of the tooth, where the crown meets the root. The tooth surface in this area consists of a bony substance called cementum, not enamel, and is more likely to decay at a faster rate. This can lead to infection of the soft tissue inside the tooth (the pulp) and the formation of an abscess (collection of pus).

It is important to receive care at an early stage of this disease in order to avoid abscesses. Treatment includes the use of techniques such as "scoop and fill," in which the bulk of the decayed material is scooped out—usually without anesthesia, using hand instruments—and replaced with a temporary filling that contains fluoride to inhibit further decay. The filling material of choice is glass ionomer. This treatment requires a dentist, who can restore each tooth in a traditional manner after the scoop and fill process. Infections of the pulp of the tooth should be treated with an antibiotic, preferably penicillin.

Anti-HIV drugs such as indinavir (Crixivan) and ddI (didanosine, Videx) may cause dry mouth. Other medications associated with the condition include interferon alpha (used to treat chronic hepatitis B and C) as well as some antidepressants, antihypertensives, antihistamines, antipsychotics, and diuretics. This does not mean that any person taking one or more of these drugs will have dry mouth followed by rampant caries, although people taking these medications should be aware that this could occur. (Dry mouth may also predispose individuals to oral candidiasis; see below.)

Fortunately, symptoms of dry mouth can be treated using simple measures. Artificial saliva products can be effective in people who have active tooth decay resulting in part from drug-related dry mouth. The frequency with which these products must be used may be unrealistic, however; it may be preferable to use sugar-free citrus candies such as lemon drops, which also stimulate saliva production.

It should be noted that small cavities can quickly become large cavities and abscesses, so early intervention and treatment is advisable.

Periodontal Disease

Periodontal disease is a chronic inflammatory process involving specific bacteria and affecting the tissue and bone supporting the teeth. While periodontal disease can occur in anyone regardless of HIV status, one particularly severe form (necrotizing ulcerative periodontitis) and a related condition (linear gingival erythema) appear to be unique to those with compromised immune systems.

The gingival (gum) condition originally known as HIV-gingivitis, and now called linear gingival erythema (LGE), consists of a red band-like lesion along the gumline. LGE may be painful and bleed, and may progress to periodontal disease (see NUP, below). LGE is sometimes mistaken for ordinary gingivitis (inflammation of the gums), which usually is not painful and does not lead to periodontal disease. People diagnosed with LGE should be given an antimicrobial mouth rinse such as chlorhexidine (Peridex) until a visit to a dentist or periodontist (a specialist in gum disease and related conditions) can be arranged. In severe cases, a systemic antibiotic may be used, though only for one week at most.

Necrotizing ulcerative periodontitis (NUP), which previously was called

HIV positive people should receive dental examinations every six months, preferably by a provider who is familiar with conditions associated with decreased immune function.

HIV-periodontitis, is a condition associated with rapid soft tissue and bone loss, including exposure of the bone; rapid deterioration of tooth attachment; and the premature loss of teeth. Bleeding and severe pain may be present. Palliative treatment (i.e., to mitigate symptoms) includes antimicrobial mouth rinses, systemic antibiotic medication, and pain medication when necessary.

Periodontal disease may go unnoticed until the tissues supporting the teeth are so damaged as to cause the loss of a tooth. Treatments include local debridement (excision of dead tissue) as well as surgical procedures and/or antibiotic medication.

Periodontal conditions should be treated without regard to HIV status. Treatment success may not be dependant upon whether or not a person is HIV positive, although some clinicians report that response to conventional therapy may be poorer in those with HIV. Preventing the premature loss of teeth due to periodontal disease is important for everyone. Like dental caries, periodontal disease is best treated at an early stage, again supporting the recommendation for routine dental examinations every six months. Notably, some research has shown smoking to be a risk factor in the development of periodontal disease.

Human Papillomavirus

Human papillomavirus (HPV), the virus associated with genital and other warts, is one of the most common sexually transmitted infections. HPV-associated lesions frequently occur in the oral cavity, including the lip and sides of the tongue. They are usually raised, dull white and fleshy, smooth or rough, and may have a cauliflower-like appearance. HPV lesions tend to be more serious and more difficult to treat in HIV positive people. A few reports also suggest that these oral lesions may be more prevalent, or the number of lesions greater, in people with HIV.

HPV lesions can be removed by surgery or other methods, such as electrocautery (burning with an electric current). The lesions usually recur, so removal should be limited to lesions that either are large enough to interfere with function, or are aesthetically displeasing.

Prevention of HPV lesions includes safe oral sexual practices. Because HPV can be transmitted through receptive oral intercourse, unprotected oral sex should be avoided if one partner has HPV. Infection with HPV, including HPV type 16 (HPV-16), leads to an increased risk of cervical and anal cancer. HPV-16 has also been associated with oral cancers (e.g., of the mouth and throat), particularly in combination with tobacco or alcohol use. (For more information on HPV, see "Anal Neoplasia," *BETA,* Winter 2001.)

Conditions Found More Often in People with HIV

The following conditions are more prevalent and can have serious consequences in HIV positive individuals, particularly those with CD4 cell counts of 500 cells/mm^3 or below. In general, the risk increases as the CD4 cell count falls.

Oral Candidiasis

Oral candidiasis (broadly known as thrush) is a relatively frequent problem for people who are HIV positive. This condition is usually associated with the *Candida albicans* fungus, and may take several different forms. Because *Candida* infection is a sign of immune dysfunction, it should be reported immediately to a medical provider.

Pseudomembranous candidiasis is by far the most common form of oral candidiasis. This condition is characterized by small, generally white patches in any part in the mouth. These patches can be easily wiped off and may be mistaken for materia alba (food particles). Sometimes there is bleeding or an erythematous (reddish) area under the white patch, and the lesion may be associated with a burning sensation or pain. People with candidiasis often notice changes in taste perception, which may make food undesirable. Oral cultures can be taken for diagnosis; however, if an HIV positive individual has had a previous *Candida* infection, it is prudent to start treatment without waiting for a culture.

There are several other less common varieties of candidiasis. One form is called angular cheilitis when it occurs at the corners of the mouth. This condition is easily mistaken for chapped lips. Topical antifungal treatment should be started without waiting for an appointment with a dentist or physician since angular cheilitis, like other forms of oral thrush, often recurs.

Erythematous candidiasis usually appears on the tongue or hard palate (the bony portion of the roof of the mouth). Lesions have a red appearance and cannot be wiped off. Atrophic candidiasis usually appears on the tongue. Both of these conditions can cause changes in taste perception and/or pain and a burning sensation.

All forms of candidiasis should be treated promptly. Treatment includes antifungal medications such as topical clotrimazole (Lotrimin) or systemic fluconazole (Diflucan). Resistant oral thrush may indicate a concurrent infection in the air sinuses alongside the nose, which may require further treatment.

Again, candidiasis is more likely to occur in individuals who have low CD4 cell counts. Dry mouth is another contributing factor. Individuals with a history of candidiasis should have antifungal medication available in the likely event that the infection recurs, particularly if immune suppression does not improve.

Aphthous Stomatitis

Aphthous stomatitis (canker sores) is a common condition regardless of HIV status. In HIV positive individuals the ulcers, or sores, may be slow to heal, and aphthous ulcers minor are more likely to become aphthous ulcers major. The difference between the two relates to ulcer size (major ulcers are over 1 cm, or 0.4 inches, in diameter) and the severity of the condition. The cause of these noncontagious lesions is not known.

Aphthous ulcers are generally shallow, crater-like lesions with a raised, red border surrounding a gray, central pseudomembrane. In HIV positive individuals these lesions may be found on keratinized (hardened) tissue such as the hard palate.

Aphthous ulcers are left to heal on their own in people with competent immune systems. However, untreated lesions may become painful, quite large, and prone to secondary infection in those with immune dysfunction. People with wasting syndrome or general debilitation may have great difficulty as these lesions may cause severe pain and decrease their ability to consume food comfortably. Accordingly, people with HIV require care for any aphthous lesions, regardless of size, to prevent them from expanding and causing potentially serious problems.

Treatment consists of a steroid medication, most frequently a topical ointment such as triamcinolone (Kenalog) or fluocinonide (Lidex) mixed with Orabase ointment. A dexamethasone liquid rinse may also be used. Some cases may require a systemic steroid such as prednisone, although the risks of systemic steroid use should be considered. Thalidomide has recently been approved in the U.S. for the treatment of aphthous ulcers, but is not commonly used because of its sedative effect.

Recurrent aphthous lesions may be mistaken for herpes simplex (see below), especially if they occur on keratinized tissue. A reliable medical history is a good method for determining the condition, since individuals with either lesion typically will have had previous episodes and often do not have both diseases.

Herpes Simplex

Oral herpes simplex is a viral condition associated with herpes simplex virus type 1 (HSV-1). It is characterized by the eruption of serum-filled vesicles, or blisters (sometimes referred to as "cold sores" or "fever blisters") on the face, lips, or mouth. (Herpes simplex virus type 2 [HSV-2] causes similar blisters in the genital or anal region.) These lesions often start with prodromal (early) symptoms of malaise, fever, and a general feeling of illness, which can be masked in people who are already ill. There also may be itching or tingling sensations. Vesicles usually form within 24 hours and rupture shortly thereafter, forming a scab. Herpes outbreaks typically resolve without treatment within two weeks in individuals with competent immune systems.

Individuals with HIV can protect themselves not only with routine examinations, but also by brushing and flossing regularly.

As with aphthous ulcers, herpes simplex lesions may be larger, more painful, and more prone to secondary infection in HIV positive individuals. Again, these lesions can exacerbate problems in people with wasting syndrome by causing pain and decreasing their ability to eat comfortably.

Palliative treatment should be provided to those with compromised immune systems. This normally involves using a systemic antiviral medication such as acyclovir (Zovirax), famciclovir (Famvir), or valacyclovir (Valtrex). In some cases, a systemic drug also may be used to suppress the recurrence of herpes lesions. Topical medications usually do not work as well as systemic medications for this condition.

Conditions Found Primarily in People with HIV

The following conditions are seen most often in people with advanced HIV disease. As with other conditions, the risk increases as CD4 cell counts decrease.

Oral Hairy Leukoplakia

Hairy leukoplakia appears as white patches, nearly always on the lateral border (outside edges) of the tongue. These lesions usually have an irregular surface and may have hair-like projections. While this condition may resemble thrush, hairy leukoplakia lesions cannot be wiped off, unlike the lesions of thrush.

Hairy leukoplakia is thought to be caused by the Epstein-Barr virus (also associated with infectious mononucleosis). Since this condition is rarely seen unless the CD4 cell count is low, it is less common in areas where combination anti-HIV therapy is readily available.

Hairy leukoplakia is a benign condition that resolves on its own. Inasmuch as it causes no symptoms, including discomfort or changes in taste perception, there is no need for treatment. For aesthetic purposes it may be treated off-label with agents

Oral HIV Treatments

CONDITION	PROBLEM	TREATMENT
Caries (cavities)		Techniques such as "scoop and fill" and temporary filling; tooth restoration
	Dry mouth (xerostomia)	Sugar-free citrus candies; artificial saliva products
	Abscess/infection of the tooth pulp	Antibiotic, preferably penicillin
Periodontal disease	Linear gingival erythema (LGE)	Antimicrobial mouth rinse such as chlorhexidine (Peridex); in severe cases, a systemic antibiotic
	Necrotizing ulcerative periodontitis (NUP)	*Palliative therapy:* antimicrobial mouth rinse, systemic antibiotic medication, pain medication *Treatment:* debridement (professional cleaning), surgical procedures, antibiotic medication
Human papillomavirus (HPV) lesions		Surgery; electrocautery; others
Oral candidiasis (thrush)	Pseudomembranous candidiasis, angular cheilitis, erythematous candidiasis, atrophic candidiasis	Topical clotrimazole (Lotrimin); systemic fluconazole (Diflucan)
Aphthous stomatitis (canker sores)		Triamcinolone (Kenalog) ointment or fluocinonide (Lidex) mixed with Orabase; dexamethasone rinse; systemic prednisone; thalidomide
Oral herpes simplex		Systemic acyclovir (Zovirax), famciclovir (Famvir), or valacyclovir (Valtrex)
Oral hairy leukoplakia		None—will resolve on its own
Opportunistic tumors	Kaposi's sarcoma (KS)	Systemic doxorubicin (Doxil) or paclitaxel (Taxol); vinblastine (Velban); localized chemotherapy; surgery; radiation therapy
	Non-Hodgkin's lymphoma (NHL)	Radiation and/or chemotherapy

such as tretinoin (Retin-A) or podophyllin.

Opportunistic Tumors

Several opportunistic tumors (cancers or neoplasms) are associated with HIV infection. Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) occur most frequently and may manifest in the oral cavity. Both of these conditions are seen when immune suppression is severe and an individual has an AIDS diagnosis (a CD4 cell count below 200 cells/mm^3).

KS is the most common neoplasm in people with HIV. It is a malignancy of the endothelial lining of blood vessels and is associated with a herpesvirus known as HHV-8. KS appears clinically as flat or raised, usually reddish or purplish lesions that do not blanch (whiten) with pressure. Lesions often enlarge rapidly and may become exophytic (grow outward).

Palliative treatment for oral KS is rarely required unless the lesion enlarges and interferes with chewing or talking. In such cases, interventions include systemic doxorubicin (Doxil) or paclitaxel (Taxol), localized chemotherapy, and surgery; injections of vinblastine (Velban) appear effective in some studies. Large, multiple lesions may be treated with radiation therapy. People with KS who start antiretroviral therapy for the first time may see their lesions resolve without further treatment.

NHL in the oral cavity is most often a soft, tumor-like mass that may enlarge rapidly. Biopsy is required for diagnosis, and treatment consists of radiation and/or chemotherapy. Until treatment can be implemented, palliative care is usually not required. (For more NHL information, see "Non-Hodgkin's Lymphoma," *BETA*, Summer 2003.)

Conclusion

HIV positive people should be encouraged to receive dental examinations every six months, preferably by a provider who is familiar with conditions associated with decreased immune function. Some conditions, such as thrush, may be mistaken for materia alba, which is the result of poor oral hygiene. Other conditions that might be allowed to run their course without medication in individuals with competent immune systems—such as aphthous ulcers—should be treated in people with HIV. Again, most oral problems, such as dental caries and periodontal disease, are the result of bacterial infections.

Individuals with HIV can protect themselves not only with routine examinations, but also by brushing and flossing regularly, as well as by not smoking and limiting alcohol intake. Smoking and alcohol use are strongly associated with oral cancers, which are relatively common and have a poor prognosis compared with other types of cancer. As always, lifestyle changes may reduce the need to fight off or treat preventable diseases.

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MOTHER-TO-CHILD TRANSMISSION

How Will AZT and Nevirapine Use for MTCT Affect Future Treatment?

Two Studies Provide Clues

Theo Smart

Two studies in the November 1, 2003 edition of the *Journal of Acquired Immune Deficiency Syndromes* [*JAIDS*] address the issue of drug resistance in women taking antiretroviral prophylaxis to prevent mother-to-child transmission [MTCT] of HIV. One found an increased risk of transmission in mothers infected with phenotypic AZT [zidovudine, Retrovir]-resistant virus. The other reported that efavirenz [Sustiva]-based regimens were as effective in women exposed to short courses of nevirapine [Viramune] as in those with no prior nevirapine exposure.

Since ACTG 076, the first study of AZT in pregnant women, dramatic progress in the prevention of MTCT of HIV has been achieved. According to an editorial accompanying the two reports, use of anti-HIV drugs by pregnant women has reduced HIV transmission by more than 70%. Today in North America and Western Europe, some studies report as few as 2% of children born to HIV positive women turn out to be HIV-infected because of antiretroviral prophylaxis and other interventions.

However, the drugs usually employed—AZT, 3TC [lamivudine, Epivir], or nevirapine monotherapy, or dual nucleoside analogues [NRTIs]—are not what anyone would characterize as optimal therapy for the mother herself. Some experts have voiced concerns that these short courses of mono- or dual therapy might lead to resistance, eventually reversing the great strides made in reducing MTCT, and even lead to increasing transmission of resistant HIV to infants. Furthermore, some worry that the development of resistance might limit any benefit that the mother or infant could one day receive from triple-drug therapy, particularly in the developing world where only a limited number of regimens are available.

The first paper reported findings from one of the oldest ongoing perinatal HIV studies in the U.S., the Women and Infants Transmission Study (WITS). This study evaluated the effect of phenotypic AZT resistance on MTCT in 74 AZT-treated mothers enrolled in the study up until September 1994. These women had moderately advanced disease, with a median CD4 cell count of 271 cells/mm^3

and a median viral load of 39,811 copies/mL. Factors independently associated with AZT resistance at delivery included previous use of AZT (before pregnancy), high viral loads, and low CD4 cell counts.

Sixteen of the women (22%) passed HIV on to their infants. After adjustment for other variables known to increase the risk of transmission (such as duration of membrane rupture at delivery), decreasing susceptibility to AZT was shown to be associated with an increased risk of transmission. These findings build on a prior WITS study that identified an increased risk of transmission in women with genotypic AZT-resistant virus (virus known to contain mutations associated with AZT resistance).

There also have been reports that transient mutations associated with nevirapine resistance have been observed in 15–19% of women six weeks after receipt of a single dose (200 mg) of nevirapine administered during delivery to prevent MTCT of HIV. Even though 12-month follow-up of these women revealed no detectable mutant virus in most cases, the rapid emergence of resistance has led to concerns over the increasingly widespread use of nevirapine to prevent MTCT in resource-limited settings.

Since no data are currently available from international MTCT programs on the effect of single-dose nevirapine on future treatment outcomes, authors of the second *JAIDS* study looked at subjects in an American cohort who had received a short course (less than 28 days) of nevirapine as part of combination therapy that was stopped due to rash or other toxicity (nevirapine resistance mutations have also been observed in such individuals). These subjects were later treated with a regimen containing efavirenz, another non-nucleoside reverse transcriptase inhibitor [NNRTI] that shares a similar resistance profile.

The subjects were drawn from the HIV Outpatient Study (HOPS) which prospectively gathers treatment data on about 3,000 patients from nine urban U.S. clinics. Responses to efavirenz in the nevirapine-pretreated subjects were compared with those of subjects with no prior exposure. Treatment success was defined as achieving viral loads below 400 copies/mL at 1–3, 4–8, and 10–14 months after starting efavirenz-based combination regimens.

Responses to efavirenz-containing regimens were compared between 26 subjects with less than 28 days of nevirapine exposure and 495 subjects with no prior reported nevirapine exposure. The demographic profiles were similar for both groups. The mean interval between stopping nevirapine and initiation of an efavirenz-containing regimen was 518 days.

There were no significant differences in the proportion with treatment success among those cases with prior nevirapine exposure of less than 28 days and those with no prior nevirapine exposure: 42% of both cases and controls achieved undetectable viral loads (less than 400 RNA copies/mL) at 1–3 months after starting efavirenz; 42% of cases and 56% of controls had undetectable viral loads at 4–8 months; and 46% of cases and 53% of controls had undetectable viral loads at 10–14 months.

The authors note that "while these U.S. findings are not directly applicable to the maternal single-dose nevirapine regimens used in international PMTCT [prevention of MTCT] programs, they do suggest that prior exposure to nevirapine may not necessarily result in higher rates of treatment failure for women later treated with efavirenz-containing regimens."

The accompanying editorial notes that follow-up studies are planned and/or underway in Uganda, Botswana, South Africa, and Thailand to assess whether women exposed to single-dose nevirapine are at increased risk of treatment failure when placed on combination antiretroviral regimens containing NNRTIs and whether viral subtype influences treatment outcome.

Additionally, the editorial's authors note that "it will also be important to carefully monitor whether there is a heightened risk of adverse events for African women who receive non-nucleoside reverse transcriptase inhibitors as part of combination treatment regimens. Enhanced risk of severe nevirapine-associated rash hypersensitivity and hepatic toxicity has been reported among women as well as among individuals with higher CD4 cell counts, and there have been several case reports of significant nevirapine toxicity among black HIV-infected pregnant women receiving chronic nevirapine therapy."

Meanwhile, it is well known that efavirenz use should be avoided in pregnant women or women at risk of becoming pregnant because of the risk of birth defects [teratogenicity]. "If high rates of nevirapine toxicity with chronic dosing were to be observed among African women, given the concerns of teratogenicity with the use of efavirenz among women of childbearing age," they conclude that "careful reconsideration would need to be given as to the optimal first-line antiretroviral therapy for women in resource-limited settings."

Theo Smart is an AIDS advocate living in South Africa.

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Insulin Resistance and Diabetes

Liz Highleyman

Metabolic complications associated with HIV disease and its treatment—including insulin resistance and diabetes, abnormal cholesterol and triglyceride levels (dyslipidemia), and body fat gain or loss—remain a medical mystery and a topic of intense interest for AIDS researchers and people with HIV alike. While these complications sometimes have been collectively referred to as "lipodystrophy syndrome," it remains unclear whether or how they are related and what causes them (see "HAART Attack: Metabolic Disorders during Long-Term Antiretroviral Therapy," *BETA*, April 1999).

Scientists are urgently trying to better understand these conditions, which may have a negative impact on quality of life, interfere with adherence to antiretroviral therapy, and lead to long-term health problems. High blood glucose levels (hyperglycemia) and dyslipidemia are a particular concern because in the population at large they have been linked with increased risk of heart disease (see "Cardiovascular Disease in People with HIV," *BETA*, Summer/Autumn 2002). Much research is underway and new clues are steadily emerging, but Daniel Kuritzkes, MD, of Boston's Brigham and Women's Hospital predicts, "We'll need several more years of follow-up to get a better perspective."

Blood Glucose Abnormalities: the Basics

The body requires sugar, or glucose, to provide energy for all its functions. A hormone called insulin allows glucose to enter individual cells. Normally, after eating, beta cells in the pancreas (an abdominal organ) produce more insulin to process the incoming sugar. Glucose and insulin levels in the blood also regulate the breakdown of glycogen (a stored form of energy) and the production of new glucose (gluconeogenesis) by the liver, as well as the release of fatty acids from fat cells (adipocytes). When normal glucose metabolism goes awry, several disorders may develop.

Insulin resistance is a condition in which the body's cells do not respond properly to the hormone and cannot take up glucose, which then builds up in the bloodstream. This causes the beta cells to release extra insulin, leading to high blood insulin levels (hyperinsulinemia). Over time, the beta cells can fail to secrete enough insulin. When the body cannot produce sufficient insulin, or the cells do not respond to it efficiently, the result is hyperglycemia—impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Eventually, this process can lead to diabetes mellitus (sugar diabetes), a condition characterized by persistent hyperglycemia (see sidebar on this page).

There are two primary forms of diabetes mellitus: type 1 and type 2. (Diabetes insipidus is an uncommon condition characterized by excess urine production unrelated to blood sugar abnormalities. Pregnant women may also develop a transient condition known as gestational diabetes. This article is limited to diabetes mellitus).

Type 1 diabetes (also called juvenile onset or insulin-dependent diabetes mellitus [IDDM]) typically occurs at a young age and is believed to result from the destruction of insulin-producing beta cells by the immune system. People with type 1 diabetes produce little or no insulin and usually must receive daily insulin injections.

Type 2 diabetes (also called adult onset, insulin-resistant, or non–insulin-dependent diabetes mellitus [NIDDM]) typically develops later in life—though it is now being seen in children—and commonly occurs in people who are overweight. (See sidebar on page 36 for more diabetes risk factors.) Type 2 diabetes is a progressive illness that involves a gradual decline in insulin sensitivity and production. It can take years or decades for mild insulin resistance to progress to full-blown diabetes, and many people with impaired insulin sensitivity never develop frank (clinically apparent) diabetes. Those with type 2 diabetes can often be treated with diet modification, increased exercise, weight loss, and/or oral medications, and usually do not require insulin injections. The blood glucose abnormalities that develop in people with HIV resemble type 2, not type 1, diabetes.

Insulin resistance and diabetes are a concern because untreated high blood sugar can lead to a wide range of long-term health problems, including kidney dysfunction, retina damage leading to blindness, nerve damage, erectile dysfunction in men, and pregnancy complications in women. In fact, diabetes is the sixth leading cause of death in the U.S. Yet these complications can occur even in people

Progression of Insulin Resistance to Type 2 Diabetes

Normal:

- Normal insulin production and cell sensitivity to insulin
- Characterized by normal blood glucose and insulin levels (fasting glucose below 100 mg/dL or glucose below 140 mg/dL after an oral glucose tolerance test)

Insulin resistance:

- Loss of insulin sensitivity and compensation by increased insulin production
- Characterized by high blood insulin levels (fasting insulin over 15 units/mL)

Impaired fasting glucose (IFG):

- Progressive reduction in insulin sensitivity
- Characterized by moderately elevated fasting blood glucose (fasting glucose 100–125 mg/dL)

Impaired glucose tolerance (IGT):

- Continued lack of insulin sensitivity and reduced ability to produce insulin to compensate for food intake
- Characterized by hyperglycemia after eating (glucose 140–199 mg/dL after an oral glucose tolerance test)

Diabetes mellitus:

- Insufficient insulin production for proper cellular functioning
- Characterized by persistent hyperglycemia both when fasting and after eating (fasting glucose over 125 mg/dL, or glucose over 200 mg/dL after an oral glucose tolerance test, or random nonfasting glucose over 200 mg/dL if accompanied by diabetes symptoms)

Risk Factors for Blood Glucose Abnormalities

- Genetic predisposition
- Family history (sibling or parent with insulin resistance or type 2 diabetes)
- Overweight or obesity (high body mass index)
- Abdominal fat accumulation, or "pot belly" (increased waist-to-hip ratio: over 1.0 for men or 0.8 for women)
- Sedentary lifestyle (minimal physical activity)
- Age over 40
- African American, Latino, Asian American, Pacific Islander, or Native American ethnicity
- History of gestational diabetes during pregnancy
- Other signs of insulin resistance syndrome (e.g., high blood pressure, dyslipidemia)
- Other signs of lipodystrophy syndrome (e.g., body fat gain or loss)
- Past tests showing insulin resistance, impaired glucose tolerance, or hyperglycemia
- History of polycystic ovary syndrome
- Use of certain medications (e.g., niacin, glucocorticoids, megestrol acetate [Megace], human growth hormone, phenytoin [Dilantin])

who never progress from impaired glucose tolerance to frank diabetes.

Hyperglycemia can also contribute to blood vessel abnormalities and cardiovascular disease, including heart attacks and strokes. This process is not well understood—especially in people with HIV—but it is thought that excess sugar in the blood may promote blood clotting and make cholesterol more likely to adhere to blood vessel walls. Both the Caerphilly Heart Study, which followed more than 2,500 men in a Welsh town between 1979 and 1983, and the Prospective Cardiovascular Munster (PROCAM) study, which followed 2,754 men, found that diabetes was associated with about a 2.5-fold increased risk of heart disease.

Insulin Resistance and HIV

Before the availability of highly active antiretroviral therapy (HAART), blood glucose abnormalities were infrequently seen in people with HIV. But in June 1997, soon after protease inhibitors (PIs) came into widespread clinical use, the U.S. Food and Drug Administration (FDA) issued a health advisory warning of an association between PIs and hyperglycemia and diabetes mellitus. Since then, there have been continued reports of insulin resistance in people using anti-HIV therapy.

Different studies have yielded widely varying estimates of the prevalence of impaired glucose metabolism in people on HAART, in part because they have used different tests and inconsistent definitions of the condition. The prevalence of frank diabetes mellitus in people with HIV is relatively low, with studies reporting rates from 0.5% to 15%. But, says Michael Dubé, MD, of Indiana University School of Medicine, diabetes is "only the tip of the iceberg." Impaired glucose tolerance is considerably more common, affecting an estimated 15–25%, and research suggests that some degree of insulin resistance may occur in one-half of people taking PIs.

Research also indicates that coinfection with the hepatitis C virus (HCV)—which affects as many as 40% of people with HIV in the U.S.—increases the risk of blood glucose abnormalities. Studies have shown that people with chronic hepatitis C are more likely to develop insulin resistance and type 2 diabetes. For example, Shruti Mehta, MPH, and colleagues from Johns Hopkins University in Baltimore found that people with HCV were four times more likely to develop type 2 diabetes than HCV negative people; however, they found no association between hepatitis B and diabetes. Mehta's team also found that HIV/HCV-coinfected people were five times more likely to develop hyperglycemia than those with HIV alone. Similarly, Michel Duong, MD, and colleagues from Dijon studied 29 HIV/HCV-coinfected individuals receiving HAART, 76 people with HIV alone, and 121 with HCV alone. Both the coinfected subjects and those with HCV alone had a significantly higher rate of insulin resistance than those with only HIV.

Although it is not clear how chronic hepatitis promotes blood sugar abnormalities, it is believed that liver damage affects the metabolism of glycogen and the production of glucose. In a letter published in the December 15, 2003 issue of the *Journal of Acquired Immune Deficiency Syndromes* (*JAIDS*), Raymond Chung, MD, and colleagues from Harvard Medical School and Massachusetts General Hospital in Boston reported that elevated alanine transaminase (ALT) liver enzyme levels—an indication of liver inflammation—predicted insulin resistance in HIV positive individuals with lipodystrophy whether or not they were coinfected with hepatitis B or C.

It is not yet known whether blood glucose abnormalities in people with HIV will have the same negative health consequences as they do in the population at large, though there is little reason to expect otherwise.

The prevalence of frank diabetes mellitus in people with HIV is relatively low, with studies reporting rates from 0.5% to 15%. But diabetes is "only the tip of the iceberg."

According to Dr. Dubé, the high prevalence of insulin resistance in people with HIV taking HAART "raises concern about the eventual development of increased cardiovascular morbidity in this population." And, say Oluwatoyin Falusi, MD, and Judith Aberg, MD, of the Adult AIDS Clinical Trials Group (AACTG) Cardiovascular Disease Focus Group, "Even if [HIV positive] patients are not at increased risk for cardiovascular disease, they are at least at the same risk as HIV negative, age-matched persons with similar risk factors."

Indeed, the prevalence of blood glucose abnormalities is substantial in the general population. An estimated 6–9% of Americans have diabetes, although rates are considerably higher among older people (20% of those over age 65) and among African Americans (13%), Latinos (10%), Native Americans (15%), and Asian Americans and Pacific Islanders. As many as one-third of Americans have some degree of insulin resistance. A recent report by the National Center for Health Statistics stated that the rate of diabetes had increased 27% between 1997 and 2002, which many attribute to the rising incidence of obesity.

Some experts have suggested that the increasing incidence of blood glucose abnormalities in people with HIV is due to the fact that, thanks to effective treatment, such individuals are now living long enough to experience the normal problems associated with aging. (Interestingly, HIV positive children on HAART rarely develop insulin resistance, although they do develop elevated blood fat levels.) But many others believe that HAART—especially PIs—or HIV itself share much of the blame.

Causes of Blood Glucose Disorders

Blood sugar abnormalities are due to too much glucose (e.g., reduced uptake of glucose by cells, increased production of glucose by the liver), too little insulin (decreased insulin release by beta cells), or some combination of both. A number of different theories have been put forth to explain the increased occurrence of insulin resistance and diabetes in people with HIV. While the bulk of research implicates PIs, other explanations cannot be discounted, and it is likely that multiple factors are at play simultaneously.

Protease Inhibitors

As noted previously, insulin resistance and diabetes were not common in people with HIV before the advent of HAART, and many studies have found an association between blood glucose abnormalities and PI therapy. In fact, PI use appears to be more directly related to disorders of glucose metabolism than to other metabolic complications such as body fat gain or loss.

Kathleen Mulligan, MD, of the University of California at San Francisco (UCSF) and colleagues analyzed data from 20 HIV positive individuals who started treatment with a PI, nine who received only nucleoside reverse transcriptase inhibitors (NRTIs), and 12 who received no antiretroviral therapy. Those who started a PI-based regimen had elevated fasting insulin and blood glucose levels, which suggest increased insulin resistance, as well as increased triglyceride and LDL ("bad") cholesterol levels. Signs of insulin resistance were apparent after an average of 3.4 months. However, no body shape changes were seen during this period. The group treated with only NRTIs did not experience similar glucose and lipid abnormalities.

Georg Behrens, MD, of Hannover Medical School in Germany and colleagues reported that 46% of 38 PI recipients in their study had impaired glucose tolerance and 13% had diabetes, compared with 24% and none, respectively, among PI-naive subjects. Ravi Walli, MD, and colleagues from Ludwig-Maximilians-Universität in Munich reported that 61% of 67 PI-treated subjects had reduced insulin sensitivity, which was seen in none of the 13 HIV positive, treatment-naive controls. Frank Goebel, MD, and colleagues, also from Munich, detected some degree of insulin resistance in 55% of people receiving PIs, compared with 27% of those receiving NRTIs, but Thierry Saint-Marc, MD, and associates from Hôpital Edouard Herriot in Lyon found that only PIs—not NRTIs—were associated with glucose abnormalities.

However, some physicians believe these insulin resistance rates are too high. "We simply do not see insulin resistance in 50% of patients taking PIs," says George Beatty, MD, MPH, of UCSF.

In the large Women's Interagency HIV Study (WIHS), women receiving PIs were significantly more likely to report that they had diabetes than HIV negative women (2.8 cases per 100 person-years vs 1.4 cases per 100 person-years, respectively). Interestingly, in this study HIV positive women who received no antiretroviral therapy or received only NRTIs were even less likely to report diabetes than HIV negative women (1.2 cases per 100 person-years).

Among the PIs, indinavir (Crixivan) has been most strongly associated with impaired glucose metabolism. Dr. Dubé and colleagues detected signs of insulin resistance in people with HIV within eight weeks of starting indinavir. Another study showed reduced insulin sensitivity as soon as two weeks after starting the drug. Mustafa Noor, MD, from the Veterans Affairs Medical Center in San Francisco and colleagues found that insulin resistance (but not elevated lipid levels or visceral fat accumulation) developed within four weeks of the 48-week study period, after increases in triglyceride and LDL cholesterol levels and abdominal fat accumulation had already occurred. Most trial data suggest that the newer PI atazanavir (Reyataz) has a minimal effect on glucose and lipid metabolism, but the drug requires further long-term study.

It is unclear exactly how PIs affect glucose metabolism, but research points to a variety of possible mechanisms, including reduced glucose uptake by peripheral cells, decreased insulin production by beta cells in the pancreas, and increased glucose production by the liver.

Several laboratory, animal, and clinical studies suggest that PIs may directly interfere with the transport of glucose into cells. An insulin-sensitive protein called Glut-4 plays a key role in transporting glucose into fat and muscle cells after eating. In laboratory studies using 3T3-L1 adipocytes (a type of fat cell), Haruhiko Murata, PhD, and colleagues from Washington University in St. Louis found that indinavir and other PIs reduced glucose uptake by inhibiting Glut-4 activity. At 100 micrometers (µm), indinavir reduced glucose uptake by 63%, while a 10 µm dose (closer to the concentrations used in humans) caused a 26% decrease. This inhibition occurred within minutes, and was reversed when indinavir was removed. In another study in frog egg cells, indinavir, amprenavir, and ritonavir (Norvir) reduced glucose uptake by 45%, 42%, and 54%, respectively. Noting that mutant mice lacking Glut-4 have almost no subcutaneous (under the skin) fat, the authors suggested that peripheral lipoatrophy (fat loss in the limbs and face) in people with HIV may be mediated by PIs' effect on the transport protein.

A related protein, Glut-2, allows beta cells in the pancreas to take up glucose to monitor blood sugar levels and regulate insulin release. Joseph Koster, PhD, and colleagues, also from Washington University, found that indinavir in doses similar to those used in humans—and other PIs at higher concentrations—inhibit the activity of Glut-2, thus reducing glucose uptake by beta cells. If the beta cells cannot detect elevated glucose levels, the authors suggest, they will not produce extra insulin to compensate, leading to hyperglycemia. These laboratory findings may help explain data from Dr. Dubé's team showing that reduced insulin sensitivity and increased fasting glucose did not trigger beta cells to release more insulin in people taking indinavir.

Proposing yet another mechanism, Dr. Capeau and colleagues found that in laboratory tests, PIs (indinavir, nelfinavir, and amprenavir) inhibit the production and activity of sterol regulatory element binding protein (SREBP), a key fat cell messenger that triggers stem cells to differentiate into adipocytes. SREBP also stimulates increased production of peroxisome proliferating activation factor gamma (PPAR-gamma), which promotes cellular glucose uptake in the presence of insulin.

Marc van der Valk, MD, from the University of Amsterdam and colleagues reported that in addition to decreased cell sensitivity to insulin, glucose production by the liver is increased in people taking PIs. Using the hyperinsulinemic euglycemic clamp technique (discussed below in the "Diagnosis and Monitoring"

While the bulk of research implicates PIs, other explanations cannot be discounted, and it is likely that multiple factors are at play simultaneously.

after starting indinavir in HIV negative volunteers. In one of their studies, glucose disposal (uptake of glucose by cells) was reduced after a single dose of the drug. Because Dr. Noor's study subjects were neither HIV positive nor taking other classes of antiretroviral drugs, these results offer evidence that indinavir itself directly triggers insulin resistance.

Some other PIs appear less likely than indinavir to cause blood glucose abnormalities. For example, Dr. Walli and colleagues found that indinavir led to greater insulin resistance than either saquinavir (Fortovase, Invirase) or amprenavir (Agenerase). At the 3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV in October 2001, Jacqueline Capeau, MD, and associates from INSERM in Paris reported that in laboratory studies, indinavir had the greatest inhibitory effect on a regulatory protein that helps control insulin resistance (discussed below), followed by nelfinavir (Viracept) and to a lesser extent amprenavir. Dr. Dubé's team saw a trend toward decreased insulin sensitivity in people treated with amprenavir, but only at the end

section), the researchers found that hepatic glucose production was 47% higher in the PI recipients than in HIV negative control subjects. In addition, insulin suppressed glucose production less in the PI group than in controls. Similarly, Dr. Noor's team found that hepatic glucose production (both gluconeogenesis and glycogenolysis, or breakdown of stored sugar) increased within four weeks of starting indinavir.

In an article in the December 2000 issue of *Clinical Infectious Diseases,* Dr. Dubé summarized the evidence for a direct effect of PIs in inducing blood glucose abnormalities. This includes the rapid development of glucose abnormalities soon after starting PI therapy, the reversal of glucose abnormalities when PIs are halted, the onset of insulin resistance before changes in body fat distribution occur, and plausible biological mechanisms. People with other risk factors for diabetes (for example, family history or obesity) may be especially susceptible to the effect of PIs on blood glucose.

Blood Glucose and Lipodystrophy

Much remains to be learned about the relationship between blood glucose abnormalities and other metabolic manifestations in people with HIV. As Dr. Dubé notes, while blood fat abnormalities, abdominal obesity, and loss of peripheral fat frequently coexist with insulin resistance, "It is not clear whether all of these result from a common pathogenic mechanism."

In the HIV negative population, glucose abnormalities, elevated triglyceride levels, decreased HDL ("good") cholesterol, high blood pressure, and visceral abdominal obesity often occur together—a syndrome variously known as insulin resistance syndrome, metabolic syndrome, or syndrome X. Here, too, it is unclear how these conditions are linked, but they occur together often enough to suggest they are interrelated.

Research indicates that altered glucose metabolism, dyslipidemia, and fat gain or loss are linked in people with HIV as well, and some researchers suggest that glucose abnormalities may in fact be attributable to body fat changes. Studies have shown, for example, that the accumulation of visceral abdominal fat can promote insulin resistance. Reduced insulin sensitivity may also result when fat cells are broken down—a process called lipolysis—as occurs during peripheral lipoatrophy. Further, research in mice suggests that loss of subcutaneous fat is associated with fat accumulation in insulin-sensitive tissues such as the liver and skeletal muscle, again contributing to insulin resistance.

Andrew Carr, MD, and colleagues from St. Vincent's Hospital in Sydney found that among people taking PIs, insulin resistance was more common in those with body shape changes—either abdominal obesity or peripheral fat loss. Dr. Carr's group also reported that people with "buffalo hump" (accumulation of fat at the back of the neck) were at higher risk for insulin resistance and diabetes, although other studies have yielded conflicting results.

Similarly, Colleen Hadigan, MD, from Massachusetts General Hospital and colleagues found that among 101 HIV positive people in the Framingham Offspring Study (a large study of cardiovascular risk), those with body fat changes were more likely to have impaired glucose tolerance (evidenced by elevated insulin levels and increased glucose levels after a glucose tolerance test) and frank diabetes. In another study, Dr. Hadigan's team found that insulin levels were most elevated in HIV positive women with abdominal fat accumulation, independent of PI use. The same research group also reported insulin resistance in men with AIDS-related wasting syndrome who were treated with NRTIs but not PIs, and noted that reduced lean body mass and increased abdominal fat were the primary predictors of hyperinsulinemia. In addition, they found that when 52 HIV positive hypogonadal (low testosterone level) men with AIDS-related wasting were given supplemental testosterone therapy, their insulin sensitivity improved as their lean body mass increased. (It should be noted, however, that supplemental testosterone may provide no additional benefit in men who already have normal levels.)

Dr. Corinne Vigouroux of INSERM and colleagues found that among study participants receiving PIs, 11 out of 14 (79%) with severe facial wasting had either insulin resistance or diabetes, compared with just four out of 20 (20%) without facial fat loss. In this study, elevated triglycerides were also more common in the group with facial wasting (79% vs 35%). Dennis Mynarcik, MD, from the State University of New York at Stony Brook and colleagues reported that among 12 HIV negative study subjects, 15 HIV positive participants with lipodystrophy, and 14 HIV positive individuals without lipodystrophy, insulin resistance was greatest in those with fat loss. Likewise, Ove Andersen, MD, and colleagues from Hvidovre University in Copenhagen reported that loss of limb fat was the strongest predictor of insulin resistance and decreased insulin production, independent of the type of antiretroviral therapy used.

Some researchers suggest that glucose abnormalities may in fact be attributable to body fat changes.

Symptoms of Hyperglycemia and Diabetes

- Increased thirst
- Increased hunger
- Copious urination
- Fatigue
- Poor concentration
- Blurred vision
- Unexplained weight loss or gain
- Slow healing of cuts and sores

Free Fatty Acids

Some research suggests that the relationship between body fat changes and glucose abnormalities may be mediated by free fatty acids. Normally, fatty acids are released when blood sugar levels are low to provide the liver with "raw material" for gluconeogenesis. High blood levels of free fatty acids—related to both visceral fat accumulation and peripheral fat loss—may interfere with normal glucose regulation and are associated with greater insulin resistance.

Dr. Hadigan's group found that HIV positive individuals receiving antiretroviral therapy (58% on PIs, 74% on NRTIs) experienced heightened fasting lipolysis that increased further after consuming glucose, an indication of reduced insulin sensitivity (normally, lipolysis decreases after glucose consumption). Those with the greatest rates of lipolysis had the most severe insulin resistance. When an agent called acipimox was used to lower free fatty acid levels, insulin sensitivity improved, but it did not return to normal, suggesting that other factors were also involved.

If the hypothesis that body fat changes promote blood glucose abnormalities holds true, PIs may play an indirect role in glucose disorders by altering lipid metabolism and causing body fat abnormalities, perhaps in addition to their more direct effect. NRTIs (especially d4T [stavudine, Zerit]) also may indirectly contribute to glucose abnormalities by causing peripheral fat loss. As noted above, Dr. Goebel and colleagues detected evidence of insulin resistance in 27% of HIV positive people treated with NRTIs (although the rate in those receiving PIs was twice as high). Dr. Mulligan, too, found that insulin sensitivity was reduced by 10% in people taking antiretroviral regimens that excluded PIs. Further, Dr. Andersen's team reported that glucose disposal was reduced in people with elevated lactic acid levels, a possible indication of NRTI-induced damage to the mitochondria, energy-producing organelles in cells that are involved in glucose metabolism.

Interestingly, research has not implicated non-nucleoside reverse transcriptase inhibitors (NNRTIs) in blood glucose abnormalities, although they have been linked with other metabolic manifestations in some studies.

Yet other data indicate that blood glucose abnormalities are not directly caused by body fat changes or dyslipidemia. Dr. Mulligan and colleagues, for example, found that blood glucose abnormalities developed just a few months after people began taking PIs, well before body shape changes occurred. Dr. Saint-Marc's team reported that when individuals with peripheral fat loss switched from d4T (which is strongly associated with lipoatrophy) to either abacavir (Ziagen) or AZT (zidovudine, Retrovir), they experienced increased subcutaneous fat but no improvement in insulin resistance.

Dr. van der Valk and colleagues demonstrated that when PIs were stopped for 96 weeks in eight HIV positive men with lipodystrophy, glucose production decreased and lipolysis was reduced, although no body fat changes were seen. In a study of diet and exercise in obese HIV positive women, Ellen Engelson, EdD, of Columbia University in New York City and associates found that after completing a 12-week weight loss program, the women experienced reductions in both visceral and subcutaneous fat, but no corresponding improvements in insulin sensitivity. And, as noted previously, HIV positive children treated with PIs develop blood lipid abnormalities, but not insulin resistance or body fat changes.

There are not yet enough data to definitively say whether body fat or blood lipid changes cause glucose abnormalities, blood sugar disorders contribute to lipodystrophy, some common mechanism underlies both manifestations, or the conditions occur together but are otherwise independent.

Other Possible Causes

Although plentiful evidence links blood glucose abnormalities in people with HIV to antiretroviral therapy with PIs (and possibly NRTIs) and body fat changes, other factors—including immune activation and HIV infection itself—may also play a role.

Some researchers have suggested that HIV may damage the beta cells in the pancreas, thus decreasing insulin production and causing impaired glucose metabolism, although little research directly supports this hypothesis. In the pre-HAART era, glucose abnormalities were sometimes seen in people taking medications such as pentamidine and ddI (didanosine, Videx), which can cause inflammation of the pancreas (pancreatitis). An early theory held that high levels of cortisol (a hormone associated with stress and chronic illness) might contribute to glucose abnormalities and other metabolic manifestations, since excess cortisol production causes Cushing's syndrome, characterized by many of the same symptoms. However, more recent research has shown that cortisol levels generally are not elevated in HIV positive people with metabolic complications.

Glucose abnormalities may also be associated with altered levels of cytokines (chemical messengers produced by cells), including tumor necrosis factor (TNF). An increased

number of TNF receptors (cell proteins that bind to TNF) is an indication of inflammation, or immune activation, which can potentially occur as HAART enables immune system recovery. Research by Dr. Mynarcik and others has shown that elevated TNF receptor levels are associated with both insulin resistance and lipoatrophy. Donald Kotler, MD, of St. Luke's-Roosevelt Hospital Center in New York City has said he believes that "TNF drives body fat changes and insulin resistance." It is possible that imbalances in other cytokines—such as interleukin-1, interleukin-6, or interleukin-10 (low levels of which are associated with autoimmune diabetes)—may also contribute to altered glucose metabolism in people with HIV.

Finally, three hormones produced by fat cells—leptin, adiponectin, and resistin—may contribute by as yet unknown mechanisms to glucose abnormalities and other metabolic complications in HIV positive and HIV negative people alike. Leptin, which helps regulate appetite, has made the news in recent years because administration of the hormone leads to weight loss in obese mice; in addition, it has been successfully used to treat people with congenital lipodystrophy. Leptin also promotes normal insulin activity. Adiponectin improves insulin sensitivity as well, while resistin inhibits the action of insulin. For example, Claire Steppan, MD, and colleagues from the University of Pennsylvania found that administration of antibodies that target resistin normalized blood glucose levels in mice. Studies have found decreased leptin and adiponectin levels in HIV positive people with body fat abnormalities. Ongoing research should shed further light on how these hormones affect metabolism and whether they can be manipulated to treat metabolic complications in humans. (See "Open Clinical Trials" on page 49 for a study of leptin in people with HIV-associated lipodystrophy.)

In summary, there is a growing consensus that multiple factors contribute to blood glucose abnormalities in people with HIV. In the words of Carl Grunfeld, MD, PhD, of UCSF, "Understanding each of these contributors and how they interact is essential to understanding the effects of therapy for HIV infection."

Diagnosis and Monitoring

Various tests may be used to diagnose blood glucose abnormalities. (See sidebar on page 35 for types of glucose abnormalities and associated laboratory values.) One common measure is fasting glucose. In this test, blood sugar is measured after a person has fasted for eight hours, with no food or beverages except water. Another test that may be used is the oral glucose tolerance test. In this assay, blood glucose is measured, the individual drinks a sugar solution (usually 75 grams) after fasting overnight, and glucose is measured again every 30–60 minutes for two hours to see if blood glucose levels rise and fall normally.

Additional tests may be done to assess hyperglycemia. The hemoglobin A1c (glucosylated hemoglobin) test measures how much glucose adheres to red blood cells, and is used to determine average blood sugar levels over the course of 2–3 months.

Assessing insulin resistance is more challenging than detecting hyperglycemia. The "gold standard" for diagnosing insulin resistance is the hyperinsulinemic euglycemic clamp technique (also known as an insulin tolerance test). In this test, a standard amount of insulin is infused intravenously, then glucose is administered until a normal blood glucose level is attained. The test is complex and expensive, and therefore tends to be used in research settings but not in routine clinical care.

Physicians may also measure fasting insulin levels. A fasting blood insulin of 15 units/mL or higher is suggestive of insulin resistance. Once the fasting insulin level is known, the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) score can be calculated. An insulin-to-glucose ratio may also be determined. However, standardized tests of blood insulin are not widely available. Because it is difficult to directly measure insulin levels, the fasting glucose and two-hour glucose tolerance tests are often used to indirectly assess insulin resistance.

In the November 1, 2002 issue of *JAIDS,* the International AIDS Society-USA (IAS-USA) published guidelines for the management of metabolic complications associated with antiretroviral therapy in people with HIV. The IAS recommends that fasting glucose should be measured before initiating HAART, 3–6 months after starting or switching drugs, and at least annually during PI therapy. People who have risk factors for blood glucose abnormalities (see sidebar on page 36), signs and symptoms of hyperglycemia (see sidebar on page 40), known impaired glucose tolerance, or severe body fat changes may benefit from oral glucose tolerance testing. Some physicians prefer regular glucose tolerance tests for all people receiving PIs. The IAS guidelines do not recommend direct monitoring of insulin levels.

Management of Blood Glucose Abnormalities

In many cases, blood glucose abnormalities can be managed by lifestyle changes, including weight loss, increased exercise, and diet modifications. These steps are usually undertaken first. Sometimes antiretroviral drugs from other classes can be substituted for PIs that promote insulin resistance. In some cases, however, antidiabetic drugs may be needed to control hyperglycemia. As noted previously, people with type 2 diabetes—the type associated with HIV and its treatment—usually do not require insulin injections.

Due to the lack of studies looking at treatment of blood glucose abnormalities in people with HIV, the IAS guidelines (compiled by a panel of 12 researchers and clinicians with expertise in metabolic complications) are similar to recommendations

Oral Antidiabetic Drug Classes

Class name	Action	How used	Side effects	Specific drugs
Biguanides	decrease glucose production by the liver, increase cell sensitivity to insulin	taken 2–3 times daily with meals	abdominal pain, nausea, diarrhea; may cause lactic acidosis; may cause kidney toxicity	metformin (Glucophage)
Thiazolidinediones (glitazones)	increase cell sensitivity to insulin, increase glucose uptake by cells	typically taken once or twice daily with food	may cause liver toxicity; may increase cholesterol levels	pioglitazone (Actos), rosiglitazone (Avandia)
Sulfonylureas	stimulate the production of insulin by beta cells, help cells use insulin more efficiently	typically taken once or twice daily immediately before meals	weight gain, gastrointestinal upset, skin rash; may cause blood sugar levels to drop too low (hypoglycemia); may cause kidney toxicity	glimepiride (Amaryl), glipizide (Glucotrol), glyburide (Micronase, Glynase), acetohexamide (Dymelor), chlorpropamide (Diabinese), tolazamide (Tolinase), tolbutamide (Orinase)
Metglitinides	stimulate the release of insulin by beta cells	taken before each meal	weight gain; may cause blood sugar levels to drop too low	repaglinide (Prandin)
Alpha-glucosidase inhibitors	inhibit the digestion of starches and certain sugars, resulting in a slower increase in blood glucose after eating	taken at the beginning of a meal	intestinal gas, bloating, diarrhea	acarbose (Precose), miglitol (Glyset)

established by the American Diabetes Association and other groups for the HIV negative population.

Only a small proportion of people with insulin resistance will go on to develop type 2 diabetes, which remains uncommon in people with HIV. It is not clear why insulin resistance progresses in some people but not others, and most physicians (and the IAS guidelines) do not recommend aggressive medical treatment for people with early-stage insulin resistance. However, because mild insulin resistance can sometimes progress rapidly to frank diabetes, regular blood glucose monitoring is important.

Lifestyle Changes

The IAS guidelines recommend a balanced diet and regular exercise regardless of the type of antiretroviral therapy a person is using. Because obesity can contribute to insulin resistance and diabetes, the guidelines also recommend maintaining a healthy body weight and losing weight if necessary—although this can be a challenge for individuals with abdominal fat gain, peripheral fat loss, or both simultaneously.

Even for people with no signs of impaired glucose metabolism and no risk factors for diabetes, maintaining a healthy weight, engaging in regular exercise, and eating a healthy diet are good practice. The Diabetic Primary Prevention Trial found that weight loss, exercise, and a healthy diet slowed the progression of hyperglycemia and delayed the onset of type 2 diabetes in an HIV negative cohort. Although these measures have not been extensively studied in people with HIV, they are potentially even more important for people taking PIs and experiencing metabolic complications. The National Institutes of Health (NIH) recommends that people exercise for at least 30 minutes each day; something as simple as regular walking can contribute to improved health.

A healthy diet is low in fat, sodium, and refined sugar, and high in fruits, vegetables, and whole grains. The American Diabetes Association recommends that carbohydrates should comprise about 50–60% of total daily calorie intake and fats should be limited to 30% or less (favoring unsaturated fats over saturated fats, hydrogenated fats, and trans fatty acids). But the type of carbohydrates consumed may be more

important than the total amount. Complex carbohydrates—starchy foods (such as potatoes, rice, corn, pasta, seeds, beans) and dietary fiber—are digested more slowly and stimulate less insulin production than simple carbohydrates (sugars, refined flour). Studies, including one by Dr. Hadigan's team in HIV positive people with lipodystrophy, have shown that dietary fiber promotes insulin sensitivity and helps maintain normal glucose levels. Moreover, research suggests that reducing calories can improve insulin sensitivity even before weight loss occurs. In HIV positive people who have problems with wasting, however, a low-calorie diet may not be appropriate.

When it comes to nutrition and HIV, more is not necessarily better. Sounding a note of caution, Grace McComsey, MD, and colleagues from Case Western Reserve University in Cleveland reported recently that in ten HIV positive, NRTI-treated individuals with lipoatrophy or lactic acidosis, administration of antioxidants (vitamin C, vitamin E, and N-acetyl cysteine) led to worsened insulin resistance and significantly elevated fasting glucose levels. These results are interesting because some past research has suggested that antioxidants may improve insulin sensitivity. Given the current climate of uncertainty, people with HIV should consult a physician—and ideally an HIV-knowledgeable dietitian—before making any major dietary changes.

Antiretroviral Selection and Substitution

Concern about blood glucose abnormalities and other metabolic complications has contributed to changes in how clinicians approach antiretroviral therapy. For example, it is now recommended that treatment be delayed in asymptomatic individuals until the CD4 cell count falls below 350 cells/mm^3 or viral load rises above 55,000 copies/mL. In addition, according to the IAS guidelines, it is reasonable to consider avoiding lipid-elevating PIs (especially as first-line therapy) in people with pre-existing glucose metabolism abnormalities or risk factors for diabetes.

For those who have already started therapy, several studies have shown that switching from PIs to antiretroviral drugs from other classes can help normalize blood glucose levels and prevent progression from insulin resistance to frank diabetes. For example, Esteban Martinez, MD, of University Hospital Clinic in Barcelona and colleagues demonstrated in two separate studies that switching from PIs to nevirapine (Viramune) or efavirenz (Sustiva) significantly improved insulin sensitivity. Similarly, Dr. Walli's team reported reduced insulin resistance when abacavir was substituted for a PI.

However, it is important that any HAART regimen maintain adequate viral suppression. For this reason, there is an emerging consensus that treatment interruptions generally should not be used to ameliorate antiretroviral side effects. Likewise, it is becoming apparent that regimens containing only NRTIs may not have enough antiviral potency. While substitution of an NNRTI for a PI to reduce insulin resistance is a reasonable approach, in some cases only a PI will provide sufficient strength. According to Jessica Justman, MD, and colleagues from the WIHS study team, "In view of the clinical benefits of PI therapy, concern about diabetes per se should not dissuade patients or practitioners from using this potent class of antiretrovirals." Fortunately, the newer PIs—particularly atazanavir—appear to be less likely than older members of this drug class to cause glucose abnormalities. As always, people with HIV should consult a physician before stopping or changing therapy.

Medical Treatment

If lifestyle changes are not adequate and eliminating PIs is not an option, several types of oral antidiabetic medication may be used to control insulin resistance and hyperglycemia (see chart on page 42). Few controlled studies of antidiabetic drugs have been completed in people with HIV, so clinical practice is based on research in the HIV negative population, taking into account what is known about side effects and interactions with other medications, including antiretrovirals. According to the IAS guidelines, metformin (Glucophage) or the thiazolidinedione (or glitazone) drugs—in particular, rosiglitazone (Avandia)—are preferred for HIV positive people with blood glucose abnormalities.

Metformin and other drugs in its class (the biguanides) work by decreasing glucose production by the liver and improving cell sensitivity to insulin. Some, though not all, studies show that these drugs may also improve body fat distribution and reduce blood lipid levels. Long-term use of metformin has been associated with a decreased risk of heart attacks in the general population. Dr. Hadigan and colleagues compared metformin with a placebo in a randomized, three-month study of 26 HIV positive people with signs of insulin resistance and body fat abnormalities. Those treated with metformin had decreased

Resources

American Diabetes Association
www.diabetes.org

National Institute of Diabetes and Digestive and Kidney Diseases
www.niddk.nih.gov/health/diabetes/diabetes.htm

Centers for Disease Control and Prevention
www.cdc.gov/diabetes

insulin levels after an oral glucose tolerance test, and also experienced significant weight loss and decreased visceral fat. There was no change in blood lipid levels. The authors concluded, "This study suggests that a relatively low dosage of metformin reduces insulin resistance and related cardiovascular risk parameters in HIV-infected patients with lipodystrophy." In another randomized study, Dr. Saint-Marc's team found that metformin improved fasting insulin levels, decreased triglyceride levels, and reduced visceral fat. However, Dr. Martinez and colleagues reported that in their study, metformin had only a minimal effect on insulin resistance, abdominal fat, and blood lipid levels.

Thiazolidinedione drugs improve insulin sensitivity. They work by activating PPAR-gamma, a cytokine that promotes the production of adipocytes and stimulates cells to take up more glucose. As with the biguanides, some studies show that the thiazolidinediones may help improve body fat distribution and normalize blood lipid levels.

In a study by Jussi Sutinen, MD, and colleagues from Helsinki University Central Hospital, 30 HIV positive subjects with lipodystrophy received either rosiglitazone or a placebo. After 24 weeks, insulin levels decreased in the rosiglitazone group but not in the placebo arm. However, triglyceride and cholesterol levels rose among those taking rosiglitazone, and there was no effect on visceral or subcutaneous fat distribution. "Rosiglitazone seemed to ameliorate insulin resistance judged by the decreased serum insulin concentrations and percentage of liver fat," the authors concluded.

Marie Gelato, MD, and colleagues from the State University of New York at Stony Brook found that in eight HIV positive individuals treated with rosiglitazone for 6–12 weeks, insulin resistance improved, as it did in Dr. Sutinen's study, but in addition visceral fat decreased and subcutaneous fat increased. Dr. Hadigan's team also found that rosiglitazone was associated with improved insulin sensitivity and increased subcutaneous fat in a study of 28 HIV positive participants, but in that study total and LDL cholesterol levels rose in the treatment arm.

Most physicians do not routinely recommend the older sulfonylurea drugs (which work by increasing insulin secretion by beta cells) for people with impaired glucose metabolism associated with antiretroviral therapy. These drugs do not directly improve insulin sensitivity and may worsen hyperinsulinemia.

Because the various antidiabetic drugs work by different mechanisms, a combination approach may be beneficial. The AIDS Clinical Trials Group is currently recruiting participants for ACTG 5082, a randomized study comparing metformin plus rosiglitazone with metformin alone or rosiglitazone alone in HIV positive people with insulin resistance and lipodystrophy (see "Open Clinical Trails" on page 50 for details).

Drug Interactions and Contraindications

Due to their potential side effects and drug interactions, antidiabetic drugs should be used with caution or avoided under certain circumstances. For example, metformin can cause lactic acidosis, a rare, life-threatening condition linked to mitochondrial toxicity associated with NRTIs (especially d4T and ddI). Therefore, people who are taking certain NRTIs or have a history or symptoms of elevated lactic acid should choose another medication or undergo careful monitoring while taking metformin. This drug should also be avoided or used with care in people with kidney problems.

The most common side effects of metformin are nausea and diarrhea (especially when the drug is first started), which could be a problem if the drug is used with antiretroviral drugs that cause similar symptoms. And, because metformin has been shown to cause weight loss, it may be a poor choice for HIV positive people with severe wasting. Conversely, for others it might be advantageous that the drug does not cause weight gain.

The thiazolidinediones can cause liver toxicity, and should be used with extreme caution and careful monitoring in people with signs of liver damage or pre-existing liver disease, including chronic hepatitis B or C. They may also present a problem for people taking antiretroviral drugs that are metabolized by the liver and are themselves associated with liver toxicity. One drug in this class, troglitazone (Rezulin), was taken off the market in 2000 after being linked to fatal liver failure. But rosiglitazone, a newer agent, appears to have less impact on the liver and fewer interactions with PIs. In a further note of caution, researchers reported in the September 9, 2003 issue of the *Mayo Clinic Proceedings* that rosiglitazone and pioglitazone (Actos) were associated with fluid buildup in the lungs and heart failure in six HIV negative men with pre-existing heart and kidney dysfunction.

Because blood glucose abnormalities and other metabolic complications often occur together in people with HIV, it is important to be aware of potential interactions between antidiabetic medications and drugs used to treat other, possibly related, conditions. For example, some research has shown that niacin (Niaspan), which is used to lower blood lipid levels, may worsen insulin resistance. People with HIV should inform their physicians and other health-care providers about all therapies they are taking, including prescription and over-the-counter medications, herbal remedies, nutritional supplements, and recreational drugs.

Conclusion

The understanding of insulin resistance, diabetes, and other metabolic complications in people with HIV has evolved rapidly in recent years, but much remains to be learned. While the exact causes of blood glucose abnormalities are not yet known, several contributing factors—including

protease inhibitors and body fat changes—have been implicated.

Fortunately, research has yielded some useful information about managing blood glucose abnormalities in HIV positive people taking antiretroviral therapy. Regular blood glucose monitoring can detect abnormalities at an early stage, before they progress to more serious conditions. Regardless of HIV status or type of therapy, lifestyle changes including weight loss (if indicated), increased exercise, and a balanced diet can make a major contribution to good health. In some cases PIs, which have been most strongly associated with blood sugar problems, can be replaced with drugs from a different class—but it is important to construct a regimen that is potent enough to maintain viral suppression. And if needed, antidiabetic medications—which are increasingly being studied in HIV positive people—are available to help control glucose and insulin abnormalities.

By working with their health-care providers to maintain a healthy blood sugar level, people with HIV can potentially prevent the development of serious long-term complications such as diabetes and cardiovascular disease.

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IN THEIR OWN WORDS

continued from page 3

only mistake is to live in the wrong part of the world. Their leaders are visionary enough to demand that the wealthy nations—we and our leaders—give everybody the same right to benefit from the progress of science. Their efforts to give the world a wake-up call deserve all our support and respect."

Mauro Guarinieri is chair of the European AIDS Treatment Group. He lives in Bologna.

Lei Chou

"What a depressing question! No, last year's crop of new anti-HIV drugs clearly demonstrated the shortcomings of a profit-based approach to clinical research and development. The three 'me-too' drugs responded to the demand of the HIV market with lower pill burden and easier dosing, but provided no significant clinical improvements such as addressing the issues of cross resistance and side effects. While T-20 [enfuvirtide, Fuzeon] does employ a new site of inhibition, it is beset by the difficulty in administration and its high cost of production, limiting its usefulness. Meaningful basic science research that is likely to find a cure is primarily done by academic and small biotech firms due to the high investment risks. Big drug companies that are profiting handsomely under the current approach of lifelong maintenance therapy have no profit incentive to change that."

Lei Chou manages the Access Project of the AIDS Treatment Data Network in New York City.

Gabe Lamazares

"I do feel that real progress is being made in the realm of combination therapy, especially in reducing pill burden, minimizing side effects, and simplifying regimens. Looking at the state of treatment even five years ago when I began therapy, I appreciate the quantum leap in treatment efficacy and tolerability. But, sorry to say, none of the advances of the past year seem to have put us any closer to a cure—a treatment that can either eradicate the virus from the system or put it into remission for a long time without daily dosing. Though we can, in many cases, keep HIV in check, we still cannot get free of it; it remains a constant companion, a time bomb that has stopped ticking for the moment. There are a few experimental 'eradication protocols' in clinical trials, but these are still shots in the dark. Where is the cure?"

Gabe Lamazares is a treatment educator and counselor at the Alliance of AIDS Services—Carolina in Raleigh.

OPEN Clinical TRIALS FOR HIV/AIDS TREATMENTS

Below is a partial listing of currently enrolling U.S. clinical trials gathered from various sources. **TrialScope** is a database of organizations that conduct HIV/AIDS-related research. It provides contact information for each research site, links to organizational web sites, the types of research conducted by each site, and any affiliations with major multicenter research groups. The federal government's **AIDSinfo** site (which replaces the former AIDS Clinical Trials Information Service and the HIV/AIDS Treatment Information Service) includes a section on clinical trials. This site features an introduction to HIV/AIDS research and study listings from the National Institutes of Health's **ClinicalTrials.gov** database of trial listings for all diseases. AIDSinfo also has a toll-free phone service at 800-874-2572. Specialists are on hand Monday through Friday from 12:00 pm to 4:00 pm ET (9:00 am to 1:00 pm PT) to help locate trials and answer questions. Like ClinicalTrials.gov, the **CenterWatch** web site also includes trial listings for all diseases including HIV/AIDS and related conditions. **Community Programs for Clinical Research on AIDS (CPCRA)** is a nationwide network that conducts community-based clinical trials. The **AIDS Community Research Initiative of America (ACRIA)** provides a listing of trials in New York, New Jersey, Connecticut, and Pennsylvania.

Call the telephone numbers listed below or see the indicated web sites for more information about specific trials and a listing of study sites. Protocol (study) numbers are provided in parentheses at the end of each trial description.

ACRIA: www.criany.org/clinical/index.html
AIDSInfo: www.aidsinfo.nih.gov/clinical_trials
CenterWatch: www.centerwatch.com
ClinicalTrials.gov: www.clinicaltrials.gov
CPCRA: www.cpcra.org
TrialScope: www.hivinsite.org/tscope

ANTIRETROVIRAL THERAPY

TMC114

This study will look at the safety, efficacy, and tolerability of TMC114, a new protease inhibitor (PI), given with low-dose ritonavir (Norvir). Laboratory research suggests that TMC114 may be effective against HIV that has developed resistance to other PIs. This Phase II trial is for treatment-experienced subjects who have taken the first three classes of anti-HIV drugs—nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and PIs. Four different doses of TMC114 will be compared. The study will include 300 participants in the U.S. and Puerto Rico and will last 48 weeks.

Eligible participants must be at least 18 years of age. They must have been on a stable (unchanged) antiretroviral regimen that does not include an NNRTI for at least eight weeks prior to the start of the study. In addition, they must previously haven taken at least one NNRTI and two PIs. They must have a viral load of at least 1,000 copies/mL, and must have evidence of at least one PI-resistance mutation. Participants may not have any active AIDS-defining illness or hepatitis A, B, or C, and must not be using any other investigational agents.

The study is being conducted at more than 50 sites, including **Atlanta** (404-616-6313), **Baltimore** (410-614-1338), **Birmingham** (205-975-7925), **Boston** (617-778-5454 ext. 223), **Chapel Hill** (919-843-8761), **Chicago** (773-296-2400 Ext. 122), **Cincinnati** (513-584-8373), **Dallas** (214-828-4702), **Denver** (303-372-5537), **Houston** (713-500-5483), **Los Angeles** (323-913-1033), **Miami** (305-695-1300), **New York** (212-305-2665), **Philadelphia** (215-615-0122), **Phoenix** (602-307-5330), **San Diego** (619-543-8080), **San Francisco** (415-292-5477 ext. 481 or 415-476-9296 ext. 336), **San Juan** (787-722-1248), **Seattle** (206-731-8877), **Tampa** (813-844-4639), and **Washington, DC** (202-745-6150); *www.clinicaltrials.gov/ct/show/NCT00071097.* (TMC114-C202)

Comparing First-Line Regimens

This open-label, randomized Phase III study will compare three different regimens in people starting anti-HIV therapy for the first time. Participants will receive either an NNRTI-based regimen (efavirenz [Sustiva] plus 3TC [lamivudine, Epivir] plus either d4T [stavudine, Zerit], AZT [zidovudine, Retrovir], or tenofovir DF [Viread]), a boosted PI regimen (lopinavir/ritonavir [Kaletra] plus 3TC plus one of the same three NRTIs), or an NRTI-sparing regimen (lopinavir/ritonavir plus efavirenz). Study visits will take place every four weeks for 24 weeks, then every eight weeks for the remainder of the 96-week study. Body measurements and DEXA scans will be done at some of the visits to assess lipodystrophy. The study aims to enroll 660 participants.

Eligible participants must be at least 13 years of age. They must have a viral load of at least 2,000 copies/mL within 60 days of study entry. Subjects are ineligible if they have previously take any anti-HIV medications for more than seven days, or if they have ever taken 3TC or an NNRTI. Current or recent use of several other medications is also excluded. Women may not be pregnant or breast-feeding.

There are more than 60 study sites, including **Atlanta** (404-616-6313), **Baltimore** (410-706-2785), **Birmingham** (205-975-7925), **Boston** (617-632-0785), **Chicago** (312-942-4810), **Cleveland** (216-778-5489), **Dallas** (214-590-0414), **Denver** (303-372-5535), **Honolulu** (808-737-2751), **Indianapolis** (317-274-8456), **Los Angeles** (310-206-8029), **Miami** (305-243-3838), **Minneapolis** (612-625-1462), **Nashville** (615-467-0154 ext. 108), **New York** (212-263-6565), **Omaha** (402-559-8163), **Pittsburgh** (412-647-0771), **Providence** (401-793-4396), **Rochester** (585-275-2740), **San Diego** (619-543-8080), **San Francisco** (415-514-0550 ext. 354), **Seattle** (206-731-8877), **Stanford** (650-723-2804), **St. Louis** (314-454-0058), and **Washington, DC** (202-687-7387); *www.clinicaltrials.gov/ct/show/NCT00050895.*
(ACTG A5142)

Once-Daily vs Twice-Daily HAART

This open-label Phase II study will compare once-daily versus twice-daily administration of antiretroviral drugs, and will also look at self-administered versus directly observed therapy. The trial is for people who are taking anti-HIV therapy for the first time. Participants will be randomly assigned to one of three study arms. All will receive the same daily dosages of lopinavir/ritonavir, FTC (emtricitabine, Emtriva), and extended-release d4T. Participants in Arm A will self-administer lopinavir/ritonavir twice daily, and FTC and d4T once daily for 48 weeks. Arm B participants will self-administer all three drugs once daily for 48 weeks. Those in Arm C will take all three drugs once daily in the presence of a clinician for 24 weeks, then by self-administration for 24 more weeks. The study will measure safety, efficacy, tolerability, and quality of life.

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

There are more than 20 sites, including **Baltimore** (410-614-4487), **Boston** (617-632-0785), **Cleveland** (216-778-5489), **Denver** (303-372-5535), **Indianapolis** (317-274-8456), **Miami** (305-243-3838), **New York** (212-263-6565), **Philadelphia** (215-349-8092), **Providence** (401-793-4396), **Rochester** (585-275-2740), **Sacramento** (916-734-8637), **San Juan** (787-767-9192), and **Seattle** (206-731-8877); *www.clinicaltrials.gov/ct/show/NCT00036452.*
(ACTG A5073)

Salvage Therapy: Dual vs Triple PIs

This study will compare a regimen containing three PIs with two different regimens containing a PI boosted with ritonavir. The trial will look at the safety, efficacy, and tolerability of the three regimens, as well as concentrations of PIs in the blood. Participants will receive either lopinavir/ritonavir (Arm A), fosamprenavir (Lexiva) plus ritonavir (Arm B), or lopinavir/ritonavir plus fosamprenavir (Arm C). Subjects in all arms will also take tenofovir plus 1–2 other NRTIs, which will not be provided by the study. Blood will be drawn periodically to assess drug pharmacokinetics. The study aims to enroll 216 subjects.

Eligible participants must be at least 18 years of age. They must previously have used at least one PI and have at least one year of total antiretroviral use. They must have been on a stable regimen for at least 12 weeks and have had a viral load of more than 5,000 copies/mL within 60 days of prestudy screening. Participants are not eligible if they have previously used both amprenavir (Agenerase) and lopinavir for more than seven days each. They must not have recently used other investigational agents, cancer chemotherapy, immune-modulating drugs, agents that may damage the kidneys, or certain other medications. Women may not be pregnant or breast-feeding, and both female and male participants must use effective contraception.

There are more than 30 study sites, including **Atlanta** (404-616-6313), **Boston** (617-726-3819), **Chapel Hill** (919-843-8761), **Chicago** (312-695-5012), **Cleveland** (216-844-8051), **Dallas** (214-590-0414), **Denver** (303-372-5535), **Galveston** (409-747-0241), **Indianapolis** (317-274-8456), **Los Angeles** (323-343-8283), **Miami** (305-243-3838), **Nashville** (615-467-0154 ext. 108), **New York** (212-263-6565), **Philadelphia** (215-349-8092), **Pittsburgh** (412-647-0771), **San Francisco** (415-514-0550 ext. 362), **Seattle** (206-731-8877), and **Stanford** (650-723-2804); *www.clinicaltrials.gov/ct/show/NCT00028366.*
(ACTG A5143)

OPTIMA: Mega-HAART and STI

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

Participants must be at least 18 years of age. They must have been on continuous HAART for at least three months, and must be on therapy at the time of enrollment. In addition, they must have experienced failure of at least two different regimens that included NRTIs, NNRTIs, and PIs, or have laboratory test results that show resistance to drugs in each of these classes. While on their current regimen, candidates' two most recent measurements must have shown a CD4 cell count of 300 cells/mm^3 or less and a viral load above 2,500 or 5,000 copies/mL (depending on the test used). Subjects are ineligible if they are unable to tolerate multiple antiretroviral drugs or have recently had certain illnesses. Women may not be pregnant or breast-feeding.

The study will be conducted at 30 Veterans Affairs medical centers, including **Ann Arbor** (734-769-7100 ext. 5797), **Baltimore** (410-605-7199), **Boston** (617-232-9500 ext. 4669), **Cleveland** (216-791-3800 ext. 4788), **Dallas** (214-857-0410), **Los Angeles** (310-268-3015), **Miami** (305-324-4455 ext. 4800), **New York** (212-951-3348), **Philadelphia** (215-823-5847), **Phoenix** (602-277-5551 ext. 6796), **San Diego** (858-552-8585 ext. 2626), **San Juan** (787-641-2904), and **St. Petersburg** (727-398-6661 ext. 5905); *www.clinicaltrials.gov/ct/show/NCT00050089*. (CSP 512)

SMART: Drug Conservation vs Viral Suppression

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

Participants must be at least 13 years of age and have a CD4 cell count above 350 cells/mm^3 within 45 days of study entry. Subjects may be using any antiretroviral or immune-modulating drugs at study entry. They must be in reasonably good health and available to continue the study for at least six months. Women may not be pregnant or breast-feeding, and both female and male participants must use effective contraception.

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

When to Change Therapy

This randomized pilot study will compare the benefits of changing antiretroviral therapy when viral load is 200 copies/mL versus waiting to switch until viral load reaches 10,000 copies/mL. The trial will look at drug resistance, viral fitness, and immune reconstitution. Current U.S. HIV treatment guidelines recommend switching to a new regimen as soon as viral load starts to rise in order to minimize the development of drug resistance. But there is evidence that some people can still benefit from therapy even after viral rebound, and delaying a regimen switch may help preserve future treatment options. Participants with viral loads between 200 and 10,000 copies/mL will be randomly assigned to switch immediately (Arm A) or switch after a delay (Arm B). Arm A participants will receive genotypic resistance testing upon study entry and, based on these results, will switch to a new regimen within four weeks. Participants in Arm B will continue their current regimen and receive resistance testing when their viral load reaches 10,000 copies/mL or more; based on the results, they will then change their regimen within four weeks. Resistance testing and regimen switching will also take place if CD4 cell counts decline by 20% from baseline. All participants will be followed for at least 48 weeks after study entry. This trial does not provide drugs.

Eligible participants must be at least 13 years of age and have been on stable HAART for at least four months. They must have a CD4 cell count of at least 200 cells/mm^3

within 45 days of study entry. Viral load must be detectable at enrollment, but must have been below 500 copies/mL prior to study screening while on the current regimen. Participants must not have certain illnesses and may not have recently used certain medications. Women may not be pregnant or breast-feeding, and subjects must be willing to use birth control.

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

When to Start HAART in People with OIs

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

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

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

SIDE EFFECTS AND OTHER CONDITIONS

Alcohol and HCV Disease Progression

This study, sponsored by the National Institutes of Health (NIH) and conducted by the University of California at San Francisco (UCSF), will examine the effects of alcohol on the progression of chronic hepatitis C (HCV). It is well known that heavy alcohol consumption (more than 60–90 grams per day) is associated with more rapid liver disease progression. This prospective study will look at the effect of smaller amounts of alcohol.

Eligible participants must have HCV, and may or may not be coinfected with HIV. Potential participants will be screened in person by study clinicians to determine eligibility. Subjects will receive a liver biopsy if they have not had one recently. Participants will be interviewed by telephone every six months about their alcohol use, and will receive an in-person interview, blood test, and physical examination annually for four years. Subjects will be compensated $25–$100 for each in-person visit and travel expenses will be reimbursed.

This study is being conducted in **San Francisco** (888-286-1821).

Leptin and HIV-Associated Lipodystrophy

This study, also conducted by UCSF, will look at whether leptin is useful in the treatment of insulin resistance, elevated blood fat levels, body fat changes, and other metabolic complications in people with HIV. Leptin is a hormone produced by fat cells that helps regulate appetite and promotes normal insulin activity. (See “Insulin Resistance and Diabetes” on page 41.)

Subjects will spend five days at San Francisco General Hospital (SFGH), where they will undergo tests of metabolism and body fat distribution. They will then receive twice-daily subcutaneous (under the skin) injections of recombinant (genetically engineered) human leptin for three months. They will then undergo another five-day testing period at SFGH. Then, the leptin dose will be increased for an additional three months, at which time subjects will undergo a final set of tests at the hospital. Brief assessments will be done between hospital stays. Subjects who complete the trial will receive $1,000 in compensation.

Participants must be between 18 and 65 years of age, have a viral load below 10,000 copies/mL within 30 days of study entry, and be on a stable antiretroviral regimen with no plans to change therapy during the six-month study. In addition, subjects must have an elevated triglyceride level (or a history of elevated triglycerides before starting lipid-lowering medication) and either peripheral (face or limbs) fat loss or abdominal fat gain. Subjects must satisfy several laboratory criteria (including liver

enzyme levels) and may not be taking hormone therapy, including hormonal contraceptives. Women may not be pregnant or breast-feeding.

The study will be conducted in **San Francisco.** Contact study coordinator Hootan Khatami, MD, at 415-206-4185.

Metformin and Rosiglitazone for Fat and Insulin Abnormalities

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

Participants must be between 18 and 65 years of age and have a viral load below 10,000 copies/mL within 30 days of study entry. They must have specific blood insulin levels and meet physical restrictions based on height, weight, and amount and location of body fat. Subjects must be on a stable anti-HIV regimen for at least 60 days prior to study entry. Participants may not have previously taken drugs to control blood sugar. They may not be taking ritonavir with either simvastatin (Zocor) or lovastatin (Mevacor). Subjects are ineligible if they have certain conditions or have recently taken certain medications. Women may not be pregnant or breast-feeding, and female and male participants must be willing to use effective contraception.

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

Blood Sugar Abnormalities in Pregnant Women

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

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

The study will be conducted at nearly 40 sites, including **Baltimore** (410-706-8933), **Birmingham** (205-558-2328), **Boston** (617-732-5635), **Chicago** (773-257-5717), **Cleveland** (216-844-8051), **Detroit** (313-745-7857), **Durham** (919-684-8216), **Honolulu** (808-737-2751), **Indianapolis** (317-274-8456), **Jacksonville** (904-244-5331), **Los Angeles** (323-226-2342), **Miami** (305-243-2154), **Minneapolis** (612-625-1462), **Nashville** (615-467-0154 ext. 105), **Newark** (973-972-3118), **New York** (212-263-6565), **Pittsburgh** (412-647-0771), **San Juan** (787-765-4186), **Seattle** (206-528-5020), **St. Louis** (314-454-0058), and **Washington, DC** (202-865-4578); *www.clinicaltrials.gov/ct/show/NCT00017797*. (ACTG A5084)

CHILDREN AND ADOLESCENTS

Weekly Drug Holidays for HIV Positive Adolescents

Few studies to date have been done in HIV positive adolescents, but as individuals infected at birth or as children reach their teen years, there is a growing need to better understand how they are affected by the virus and its treatment. This Phase II study will look at whether taking antiretroviral therapy on a four-days-on, three-days-off schedule can control HIV in 160 adolescents infected during childhood who have successfully maintained viral suppression with full-time therapy for at least six months. The study is motivated by concern about the cumulative effects of anti-HIV therapy and a desire to develop simpler regimens for teens.

Participants will be randomly assigned to receive either short-cycle therapy with three days off drugs each week, or standard continuous HAART. Subjects will be seen every other week for the first month, then monthly until the end of the 24-week study. HIV viral load and CD4

cell count will be assessed at every visit. Triglyceride and cholesterol levels will be measured at the beginning and the end of the study.

Eligible participants must be between 12 and 24 years of age and have been infected with HIV after age 9 (those infected perinatally are not eligible). They must have been on a stable antiretroviral regimen containing a PI but no NNRTIs or abacavir (Ziagen) for at least three months before study entry. In addition, they must have had three viral load measurements below 400 copies/mL within the past year, no measurements above that level within the past six months, and a viral load below 50 copies/mL within 30 days of study entry. They must also have a CD4 cell count of at least 350 cells/mm^3. Participants are not eligible if they have certain illnesses or have recently taken certain medications. Females may not be pregnant, and subjects must be willing to use contraception.

The nine study sites are **Chicago** (312-572-4571), **Fort Lauderdale** (954-728-1125), **Los Angeles** (323-660-2450 ext. 3914), **Miami** (305-243-3442), **New York** (212-423-2867), **Philadelphia** (215-590-4954), **San Diego** (619-543-8080), **San Juan** (787-759-9595), and **Washington, DC** (202-884-3714); *www.clinicaltrials.gov/ct/show/NCT00068809*. (ATN 015)

Metabolic Abnormalities in Young Women

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

Eligible participants must be females between 12 and 24 years of age. Both HIV negative and HIV positive participants are eligible; those with HIV may be taking any type of antiretroviral therapy or none at all. Subjects are not eligible if they have type 1 diabetes or type 2 diabetes that must be controlled with daily drugs. Participants may not be pregnant currently or within the past year.

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

Metabolic Manifestations in Children and Adolescents

Two currently enrolling studies will look at metabolic effects of antiretroviral therapy in HIV positive children and adolescents. Research to date is conflicting as to whether anti-HIV drugs are associated with blood glucose abnormalities, elevated blood lipid levels, and/or body composition changes in children and adolescents with HIV.

I) The first study will look at how starting or changing anti-HIV therapy affects the growth and body composition of HIV-infected children, as well as the relationship between body composition, HIV viral load, and CD4 cell count. In addition, the study will examine cytokine (chemical messenger) levels and how these relate to body composition. This observational study will enroll children in four different age groups: 1 month to 18 months, 18 months to 3 years, 3 years to 8 years, and 8 years to 13 years. Participants will have five clinic visits, which will include anthropometric measurements; body composition assessment using bioelectrical impedance analysis; and blood tests for viral load, CD4 cell count, and markers of lipid and glucose metabolism.

Eligible children must be 1 month to 12 years of age and not yet have begun puberty. They must either be antiretroviral naive and starting anti-HIV therapy for the first time, be PI naive and starting PIs for the first time, or be changing to a new antiretroviral regimen that contains at least two drugs not previously used. Children are not eligible if they have certain disabilities or illnesses, including insulin-dependent diabetes, or have recently used certain medications.

The study is being conducted at 50 sites, including **Baltimore** (410-706-8933), **Birmingham** (205-558-2328), **Boston** (617-355-8198), **Chicago** (773-880-3669), **Denver** (303-861-6751), **Durham** (919-684-6335), **Houston** (832-824-2583), **Los Angeles** (323-226-2342), **Memphis** (901-495-2004), **Miami** (305-243-4447), **Newark** (973-972-3118), **New Haven** (203-688-6093 ext. 3498), **New York** (212-939-4045), **Oakland** (510-428-3885 ext. 2827), **Phoenix** (602-239-5261), **San Diego** (619-543-8080 ext. 236), **San Juan** (787-765-4186), and **Washington, DC** (202-865-1248); *www.clinicaltrials.gov/ct/show/NCT00006064*. (PACTG P1010)

II) The second study will measure insulin resistance in HIV positive children and adolescents taking PIs compared with those not taking this class of drugs. Children and adolescents starting PIs will be followed for two years to assess changes in insulin sensitivity. The study also will look at whether protein turnover (metabolism and utilization of proteins from food) and growth are affected by PI use.

Eligible participants must be between 7 and 18 years of age. Both HIV negative and HIV positive children and adolescents may join the study. Those with HIV may be either antiretroviral naive or experienced. Subjects may not have recently used certain medications, including steroids.

There are two study sites, **Houston** and **Salt Lake City.** Contact study coordinator Julie Rice at 801-585-9837; *www.clinicaltrials.gov/ct/show/NCT00004739*. (NCRR-M01RR02558)

glossary

A

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

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

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

ASYMPTOMATIC:
showing no outward signs of a disease.

B

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

BETA CELL:
an insulin-producing cell located in the islets of Langerhans in the pancreas.

BODY MASS INDEX (BMI):
a measure of body mass that is calculated as weight divided by height squared.

C

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

CCR5:
a protein found on certain cells that functions as a coreceptor that enables HIV to enter the cells. Individuals who lack two functional copies of the gene that makes CCR5 are believed to be less susceptible to HIV infection.

CD4 CELL (CD4 LYMPHOCYTE, T-HELPER CELL):
a type of white blood cell that bears the CD4 surface receptor and helps the body fight infection.

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

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

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

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

CONGENITAL:
present from the time of birth.

CONTRAINDICATED:
refers to a drug or other treatment method that is inadvisable.

CORECEPTOR:
a second cell surface receptor required for entry by a pathogen into a host cell or for initiation of a biological process. HIV requires both the CD4 receptor and a coreceptor (e.g., CCR5 or CXCR4) to enter a cell.

CULTURE:
a method of growing a microorganism or living tissue *in vitro* in a medium that promotes its growth.

CXCR4:
a coreceptor on the surface of certain T cells that, along with the CD4 receptor, allows HIV to infect a cell.

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

D

DIABETES MELLITUS:
a disease caused by insufficient insulin production or lack of responsiveness to insulin, leading to hyperglycemia (high blood glucose). There are two primary types of diabetes mellitus: type 1 (also called juvenile onset or insulin-dependent diabetes mellitus [IDDM]) and type 2 (also called adult onset, insulin-resistant, or non–insulin-dependent diabetes mellitus [NIDDM]).

F

FIRST-LINE TREATMENT:
the preferred standard therapy for a particular condition.

FRANK:
clinically apparent.

G

GASTROINTESTINAL:
relating to the stomach and intestines.

GENE (*adjective* GENETIC):
the unit of heredity. Genes determine many aspects of anatomy and physiology by controlling the production of proteins.

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

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

H

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

HEPATITIS B (HBV):
an infectious viral disease of the liver that may be acute or chronic. Chronic hepatitis B can lead to liver damage, cirrhosis (scarring), and/or cancer.

HEPATITIS C (HCV, *formerly* NON-A, NON-B HEPATITIS):
an infectious viral disease of the liver. Most infected individuals develop chronic hepatitis C, which can lead to life-threatening liver damage, cirrhosis, and/or cancer.

HORMONE:
a chemical messenger (e.g., adrenaline, testosterone) involved in the regulation and coordination of cellular and bodily functions.

HYPERGLYCEMIA:
high blood sugar (glucose).

I

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

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

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

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

INTENT-TO-TREAT ANALYSIS (ITT ANALYSIS):
a method of examining the results of a clinical trial in which all participants, including those who dropped out, are analyzed according to the original randomization. An ITT analysis is more clinically useful than an as-treated analysis, which considers data only from subjects who remained in a given study.

INTRAVENOUS (IV):
injected into a vein.

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

L

LACTIC ACIDOSIS:
a life-threatening buildup of lactic acid (a by-product of carbohydrate metabolism) in bodily tissues.

LEAN BODY MASS:
muscle and organ tissue.

LIPODYSTROPHY:
body fat abnormalities, which may include wasting and localized fat accumulation. May also refer to a broader, poorly defined syndrome that may include altered fat metabolism, insulin resistance, and other manifestations.

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

LYMPHOMA:
cancer of the lymphoid tissue. Lymphomas are classified as Hodgkin's disease or non-Hodgkin's lymphoma (NHL); NHL is more common in people with HIV/AIDS.

M

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

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

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

MORBIDITY:
sickness; the state of being affected by disease.

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

O

OBESITY:
an abnormal accumulation of fat; corpulence.

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

P

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

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

PATIENT-YEAR:
a shorthand term used by epidemiologists to make comparisons. Its value is determined by multiplying the number of patients by the number of years. For example, one person followed for ten years or ten persons followed for one year both equal ten patient-years.

PEGYLATED (PEG):
refers to a drug encased in a fat molecule called polyethylene glycol, which slows metabolism of the drug in the body.

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

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

PLAQUE:
a film of food particles and other substances that is deposited on teeth and promotes bacterial growth.

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

PSEUDOMEMBRANE:
a tough, thick material on a mucosal or skin surface.

PSYCHOSOCIAL:
relating to mental health and social conditions.

R

RESISTANCE:
the mutation of a microorganism in such a way that it loses its sensitivity to a drug; a resistant organism can function and replicate despite a drug's presence.

S

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

STEM CELL:
a precursor cell in the bone marrow from which all blood cells are derived. As they mature, stem cells evolve into red and white blood cells and platelets.

SUBCUTANEOUS:
beneath the skin; subdermal.

SYMPTOMATIC:
showing outward signs of a disease.

T

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

U

UPTAKE:
incorporation or absorption of an agent into a cell or a living organism.

V

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

VISCERA (*adjective* VISCERAL):
the major internal organs of the body (e.g., intestines, liver) located in the abdominal cavity.

W

WAIST-TO-HIP RATIO:
a body shape measurement that describes the relationship between waist circumference and hip circumference. For example, a waist measurement of 36 inches and a hip measurement of 40 inches results in a waist-to-hip ratio of 0.90 (36 / 40 = 0.90).

SF

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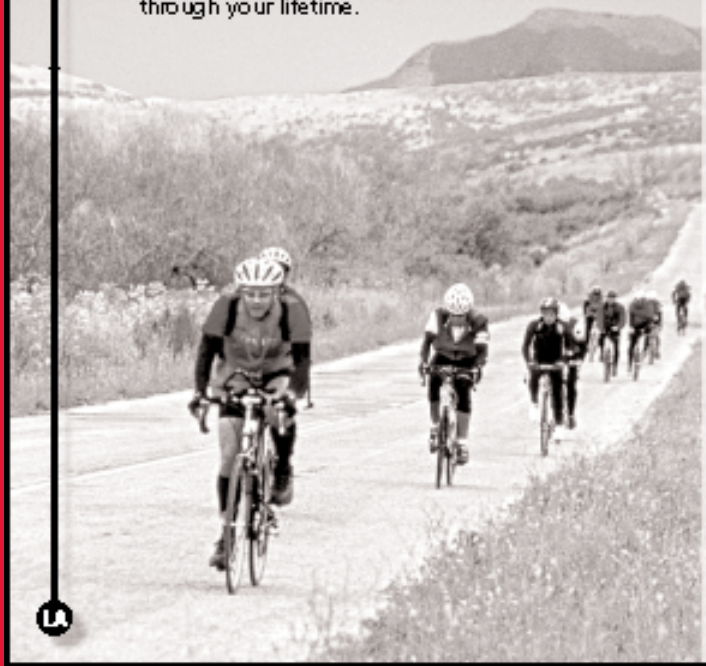

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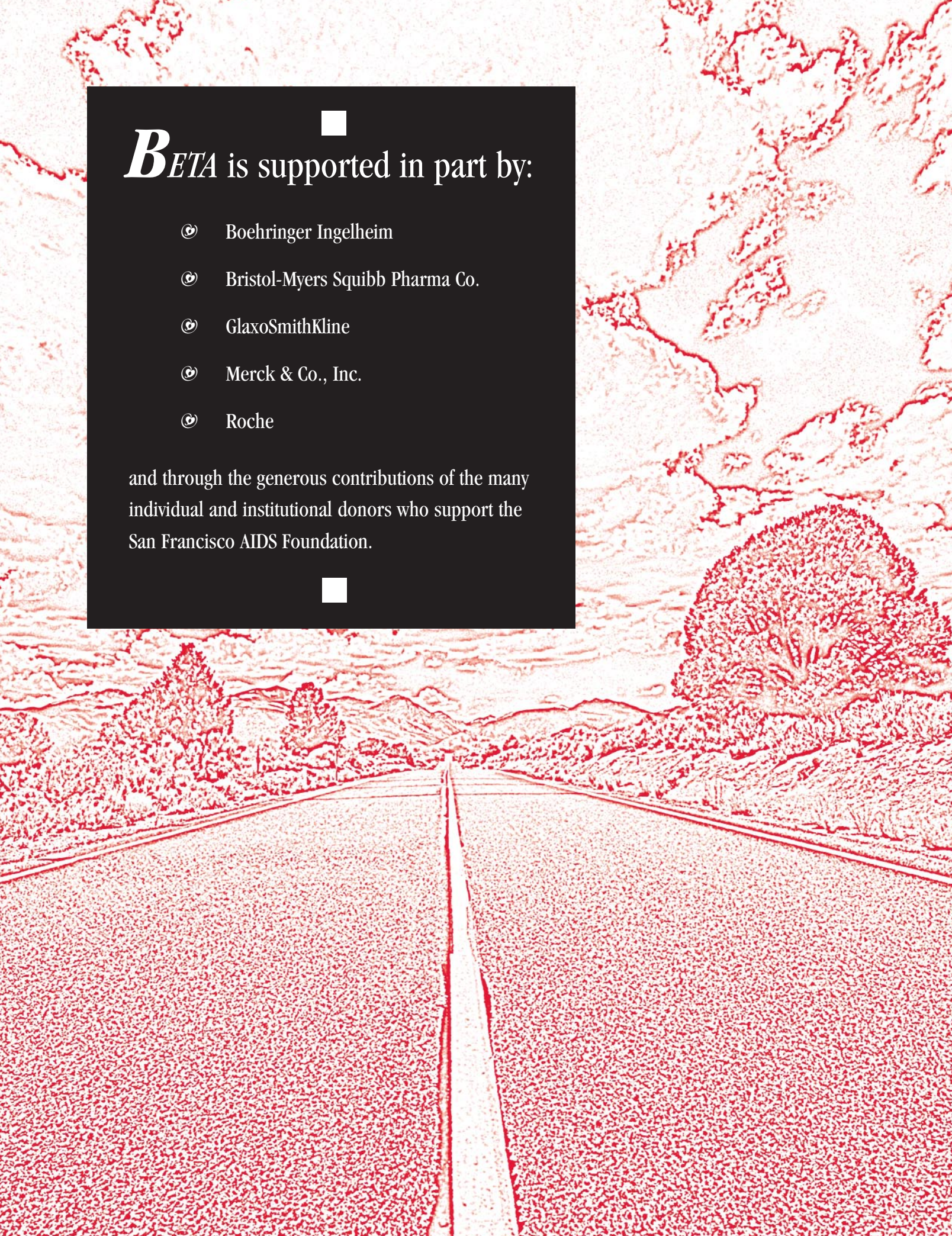

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