



Liz
Highleyman

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

Three major HIV/AIDS conferences have taken place since the last issue of *BETA*: the 16th International AIDS Conference, held August 13–18 in Toronto; the annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held September 27–30 in San Francisco; and the 8th Congress on Drug Therapy in HIV Infection (HIV8), held November 12–16 in Glasgow.

The International AIDS Conference—the largest ever, with more than 24,000 participants—emphasized global access to treatment and HIV prevention

(see “New Approaches to HIV Prevention,” page 29), but also included numerous presentations on the latest antiretroviral treatment strategies and investigational agents. ICAAC and HIV8 are more specialized meetings devoted to medical management of HIV disease, including HIV/hepatitis coinfection.

Due to the large amount of information presented at these meetings, *BETA*'s news summary is necessarily incomplete; for more, see the Web sites listed below.

O N T H E W E B

16th INTERNATIONAL AIDS CONFERENCE:

www.aids2006.org

HIV8:

www.abstracts2view.com/hiv

ICAAC:

www.icaac.org

RYAN WHITE FUNDING REAUTHORIZED

After more than a year of delay and debate, on December 9, the 109th Congress reauthorized the Ryan White CARE Act for an additional three years. The compromise bill resolves an ongoing dispute between states (such as California and New York) that encompass the urban centers that bore the brunt of the early HIV/AIDS epidemic, and Southern and rural states that have been more heavily impacted in recent years. Cities such as San Francisco and New York feared the loss of established programs without continued funding, while rural areas claimed they received less money per HIV/AIDS case than the original epicenters.

The final legislation shifts some money to smaller states, while strengthening a “hold harmless” provision that allows better-funded states to receive at least 95% of their 2006 funding levels. All people diagnosed with HIV will be counted when determining funding allocations, regardless of how data are reported, and a four-year transition period will permit states with code-based reporting systems to switch to names-based reporting without penalty. The compromise measure will provide funding for three years, rather than the usual five-year

authorization period, to force legislators to restructure the program sooner.

CDC ISSUES NEW HIV TESTING RECOMMENDATIONS

In late September, the U.S. Centers for Disease Control and Prevention (CDC) published new recommendations urging health-care providers to make HIV antibody testing a routine part of medical care for all individuals aged 13 to 64, with an opt-out provision. Under previous guidelines, testing was only recommended for individuals with specific risk factors. The CDC also loosened requirements for pre-test counseling and written consent for HIV testing, bringing it more in line with procedures for other infectious diseases (see “In Their Own Words,” page 3).

“These new recommendations will make routine HIV screening feasible in busy medical settings where it previously was impractical,” said the CDC’s Kevin Fenton, MD. “Making the HIV test a normal part of care for all Americans is also an important step toward removing the stigma still associated with testing.”

The CDC estimates that some 250,000 HIV positive people in the U.S. do not know they are infected, and

Three new expanded access programs are or soon will be available to provide drugs to individuals who lack viable treatment options.

therefore do not take advantage of early treatment or take precautions to prevent transmission of the virus. Studies have shown that nearly 40% of people test positive for HIV within a year of progressing to AIDS, and people who are unaware of their serostatus may account for as many as 70% of new sexually transmitted HIV infections.

The “Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings” were published in the September 22, 2006, issue of the *CDC’s Morbidity and Mortality Weekly Report*.

NEW POLICY FOR HIV POSITIVE VISITORS TO U.S.

To mark World AIDS Day on December 1, the White House announced that President George W. Bush would issue an executive order lifting the requirement that HIV positive foreign visitors must obtain a special waiver to enter the U.S. For 20 years, HIV has been included in a list of “dangerous contagious diseases” used to prohibit people from obtaining visas, permanent residency, or U.S. citizenship. HIV positive visitors could apply for a waiver, but this entailed a cumbersome application process, an often lengthy waiting period, and a permanent passport stamp revealing one’s HIV status.

Under the new policy, HIV positive visitors will be able to obtain a “categorical waiver” for business or tourist visas for up to 60 days; it is not yet clear whether such individuals will still be required to declare their HIV status. “We applaud President Bush for his order rescinding this outright ban on HIV positive foreigners entering the United States,” said AIDS Healthcare Foundation president Michael Weinstein. “Although we would like to see an even more enlightened approach on this issue, this executive order is a vast improvement over current law.”

UPDATED HIV TREATMENT GUIDELINES

On October 10, the U.S. Department of Health and Human Services (DHHS) issued an updated version of its “Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.”

Among the major changes are the addition of boosted atazanavir (Reyataz) and fosamprenavir (Lexiva) to the list of preferred components of first-line regimens, along with lopinavir/ritonavir (Kaletra) and efavirenz (Sustiva). Tenofovir DF (Viread) plus emtricitabine (Emtriva) and AZT (Retrovir) plus 3TC (Epivir) remain the preferred first-line nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbones. Nelfinavir (Viracept), boosted saquinavir (Invirase), and the triple-NRTI combination AZT/3TC/abacavir (Trizivir) were removed from the list of alternative first-line components,

although they may still be appropriate for selected patients.

In addition, the panel added new data about the recently approved protease inhibitor (PI) darunavir (Prezista) and the fixed-dose tenofovir/3TC/efavirenz combination pill (Atripla), as well as new safety information regarding intracranial hemorrhage in patients taking tipranavir (Aptivus).

The same month, the National Institutes of Health issued updated “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection.” Changes include revised recommendations on when to initiate therapy in treatment-naïve children, treatment of HIV positive adolescents, and the addition of information about newly approved drugs.

Finally, the Public Health Service Task Force updated its “Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States.” This revision includes new pharmacokinetic and toxicity data for various antiretroviral agents.

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

THREE NEW EXPANDED ACCESS PROGRAMS AVAILABLE

Three new expanded access programs (EAPs) are or soon will be available to provide experimental antiretroviral agents to treatment-experienced individuals who lack viable treatment options.

In August, Merck opened an EAP for its experimental HIV integrase inhibitor, MK-0518 (see news item, page 6). Participants will receive 400 mg twice-daily MK-0518 plus optimized background therapy (OBT). To qualify for the program, known as EARMRK, individuals must have documented resistance or intolerance to at least one drug in each of the three major antiretroviral classes, and must be on a failing regimen and at risk for clinical or immunological disease progression. OBT regimens should include two new drugs to which a patient’s virus remains susceptible, and participants may combine MK-0518 with investigational antiretroviral agents available through other companies’ EAPs. For further information and exclusion criteria, see www.earmrk.com or call 1-877-EARMRK1.

In September, Tibotec initiated an EAP for its investigational non-nucleoside reverse transcriptase inhibitor (NNRTI) TMC125. Participants will receive 200 mg twice-daily TMC125 in combination with an investigator-selected

OBT regimen. Eligible individuals may be either on a failing regimen or undergoing a treatment interruption, and must have prior experience with at least two PI-containing regimens, exposure to at least three classes of antiretroviral drugs, or past experience with PIs and NRTIs plus inability to use approved NNRTIs due to resistance or intolerance. This EAP will serve as an open-label Phase III clinical trial (TMC125-C214). For further information, exclusion criteria, and enrollment sites, see www.clinicaltrials.gov/ct/show/NCT00354627.

Finally, Pfizer announced in late November that it would open an international EAP for its investigational CCR5 antagonist, maraviroc, which is currently undergoing Phase III trials. Pending regulatory approval of the EAP protocol, the company expects to begin enrollment within the first quarter of 2007. Study patients will receive open-label maraviroc twice daily in addition to OBT. Eligible participants must have CCR5-tropic HIV and have limited or no treatment options due to drug resistance or intolerance. Check www.pfizer.com for updates.

FDA APPROVES ATAZANAVIR 300-MG SINGLE-CAPSULE FORMULATION

The U.S. Food and Drug Administration (FDA) in October approved a new 300-mg single-capsule formulation of atazanavir (Reyataz) for use in combination antiretroviral therapy. The new formulation is the first one-pill, once-daily PI dosing option, and is intended for use with a boosting dose of ritonavir (Norvir). The new 300-mg capsule can be used in place of two 150-mg capsules in treatment-experienced individuals and patients whose regimens also include tenofovir.

GSK DISCONTINUES DEVELOPMENT OF BRECANAVIR

On December 18, GlaxoSmithKline (GSK) announced that it would discontinue its work on brecanavir (GSK 640385), an investigational PI the company was developing in collaboration with Vertex Pharmaceuticals. Although the drug had reached Phase II trials, GSK cited “insurmountable issues regarding formulation,” saying it was unable to develop an oral formulation capable of delivering desired drug levels in patients with multidrug-resistant HIV. “We conducted extensive studies in an effort to identify a formulation that would maximize therapeutic benefit for people living with HIV, especially those who are heavily treatment experienced,” GSK said in a statement to HIV patient advocates. “Ultimately, our formulation work could not overcome the limitations of the brecanavir molecule which make consistent delivery of target drug levels unachievable.” The company said it would work with investigators to

identify and implement alternative treatment arrangements for current clinical trial participants.

MORE PROMISING DATA ON MK-0518

At the 2006 Conference on Retroviruses and Opportunistic Infections, researchers presented data showing that the integrase inhibitor MK-0518 was effective in treatment-experienced patients with drug-resistant virus (see “MK-0518 and GS-9137: Two Promising Integrase Inhibitors in the Pipeline,” *BETA*, Summer 2006). At the International AIDS Conference, Martin Markowitz, MD, presented late-breaking results showing that the drug also suppresses HIV in individuals receiving treatment for the first time (*abstract THLB0214*).

In a double-blind Phase II trial, 198 treatment-naive participants with HIV viral loads of at least 5000 copies/mL and CD4 cell counts of at least 100 cells/mm³ were randomly assigned to receive one of four doses of MK-0518 (100, 200, 400, or 600 mg twice daily) or else efavirenz; all participants also took tenofovir and 3TC. HIV RNA levels fell rapidly, with viral load decreasing by more than 2 logs in all MK-0518 dose arms. A similar proportion of patients achieved HIV suppression below 50 copies/mL in the MK-0518 arms (85%–95%) and the efavirenz arm (92%) by week 16, and the reduction was maintained at week 24. CD4 cell increases were similar across all arms, ranging from 75–135 cells/mm³. The study drug was generally well tolerated, with similar rates of severe adverse events in the MK-0518 and efavirenz arms (4% vs 3%). The study will continue through 96 weeks.

Several studies presented at ICAAC provided further information on this new agent. One analysis (*abstract A-372*) showed that MK-0518 does not inhibit or induce cytochrome P450 enzyme activity, suggesting that it will have limited interactions with other antiretroviral agents. Three small studies (*abstracts A-373, A-374, A-375*) demonstrated that MK-0518 was well tolerated and did not produce significant interactions when administered with ritonavir, efavirenz, ritonavir-boosted tipranavir, or tenofovir. Finally, researchers showed that MK-0518 at doses of 100 mg–600 mg twice-daily plus tenofovir did not increase serum total cholesterol or triglyceride levels, unlike efavirenz (*abstract H-256a*).

Merck expects to file for approval of MK-0518 later this year.

SMART DATA CONFIRM RISK OF TREATMENT INTERRUPTION

Treatment interruption is a risky strategy, according to data from the large international SMART study. Results from SMART were first reported at the 2006 Retrovirus

conference (see “Structured Treatment Interruptions: After SMART,” *BETA*, Summer 2006). Further data were presented at the International AIDS Conference (*abstracts WEAB0203, WEAB0204, THPE0047, THPE0145*), and complete findings were published in the November 30, 2006, issue of the *New England Journal of Medicine*.

The international trial included 5472 HIV positive adults with initial CD4 cell counts above 350 cells/mm³. One group was randomly assigned to defer antiretroviral therapy as long as CD4 cell counts remained above this level, and to start treatment when counts fell below 250 cells/mm³ (drug conservation arm). The rest received continuous therapy (viral suppression arm). The drug conservation arm was prematurely discontinued in January 2006 after it became apparent that these participants had more than twice the risk of opportunistic illnesses (OIs) and death.

Within two months of interrupting therapy, the percentage of participants with viral loads below 400 copies/mL decreased from 71.8% to 6.0% in the drug conservation arm. On average, the CD4 count was 206 cells/mm³ lower in this group. OIs or death due to any cause occurred in 120 participants (4.4%) in the drug conservation arm, compared with 47 (1.7%) in the continuous therapy group (3.3 vs 1.3 per 100 person-years, respectively). While the increased OI rate was not surprising, participants in the drug conservation arm also had an unexpectedly higher rate of cardiovascular, kidney, and liver problems, which are often assumed to be associated with antiretroviral therapy. The elevated risk of disease and death in the treatment interruption arm was particularly pronounced among individuals with higher CD4 cell counts and lower viral loads before study entry. These findings “provide clear and compelling evidence” that CD4-guided treatment interruption is deleterious, concluded authors Waafa El-Sadr, MD, and colleagues.

Much—but not all—of the difference in the rate of OIs and death in this study could be explained by differences in CD4 counts and viral loads during follow-up. At the Toronto conference, coauthor Jens Lundgren, MD, said there must be a “missing link” to explain the higher risk of adverse outcomes among individuals undergoing treatment interruption. Some experts have speculated that chronic inflammation associated with HIV infection, or perhaps some type of immune impairment not reflected in the CD4 count, may play a role.

At the same meeting, another research team presented data from the DART study (*abstract THLB0207*), which was also prematurely discontinued in 2006. In this trial, conducted in Uganda and Zimbabwe, 813 treatment-naïve participants who reached CD4 counts above 300 cells/mm³

after 48 or 72 weeks of antiretroviral therapy were randomly assigned to continue treatment or to interrupt and re-initiate therapy in 12-week cycles. Twelve patients in the continuous therapy arm developed new or recurrent AIDS-defining illnesses or died, compared with 31 in the treatment interruption arm (3.2 vs 8.2 per 100 person-years, respectively). Although most participants were able to take intermittent antiretroviral therapy without developing AIDS-defining events, treatment interruption was associated with a 2.6-fold increased risk of disease progression, leading the researchers to conclude that this strategy “cannot be recommended.”

Two other recent studies also cast a dim light on a different treatment interruption strategy, in which individuals on failing therapy with highly drug-resistant HIV take a treatment break in the hope that their virus will revert to a drug-susceptible “wild-type” strain before resuming therapy. In the October 2006 *Journal of Acquired Immune Deficiency Syndromes (JAIDS)*, investigators with the CPCRA 064 study reported that for patients with multidrug-resistant HIV, treatment interruption before changing regimens “does not confer any apparent benefits with regard to virological response or delayed disease progression” and “has a prolonged negative impact on CD4 cell count recovery.” Likewise, in the November 1, 2006, *Journal of Infectious Diseases*, Constance Benson, MD, and colleagues reported that in the ACTG A5086 study, a 16-week interruption of failing therapy before starting an optimized regimen did not improve virological response, and that multidrug-resistant HIV re-emerged soon after resuming treatment.

However, as reported in the August 5, 2006, issue of *The Lancet*, data from the Staccato trial showed that individuals who underwent treatment interruption using a higher CD4 cell threshold did not experience more AIDS-defining events. This study, conducted by the HIV Netherlands Australia Thailand Research Collaboration, included 430 participants with initial viral loads below 50 copies/mL and CD4 cell counts greater than 350 cells/mm³. Participants were randomly assigned to either receive continuous therapy or stop treatment until their CD4 counts fell below this level. More than 90% of participants in both arms maintained undetectable viral loads after a median 22 months of follow-up. No AIDS-defining events or HIV-related deaths occurred in either arm, and emergence of drug resistance was similar between arms. But treatment-related adverse events occurred more frequently in the continuous therapy arm, while the treatment interruption group had lower CD4 cell counts and more minor manifestations of HIV infection, such as candidiasis. Based on these findings, the researchers suggested that treatment interruption with

careful CD4 count monitoring may be a viable strategy for selected patients.

PROTEASE INHIBITOR MONOTHERAPY

In an effort to simplify antiretroviral therapy and avoid long-term toxicities, researchers have explored less-complex regimens, including monotherapy using a single boosted PI. This strategy was discussed in “Revisiting Monotherapy: Heresy or Revised Orthodoxy?” in the Winter 2006 issue of *BETA*.

At the HIV8 meeting in Glasgow, two research teams presented further data on lopinavir/ritonavir monotherapy. Joseph Gathe, MD—one of the first to explore the PI monotherapy strategy—presented long-term follow-up data from the IMANI I trial (*abstract P62*), which included 30 antiretroviral-naïve participants who started single-agent therapy with lopinavir/ritonavir. By week 48, 10 patients had discontinued therapy. The remaining 20 patients (18 of whom stayed on monotherapy and two of whom added tenofovir) all had HIV viral loads below 400 copies/mL by week 48, and 90% had viral loads below 50 copies/mL. At the time of the report, 15 of the 18 monotherapy patients had remained under observation for 152–216 weeks; 14 had HIV RNA levels below 50 copies/mL at the last measurement (though seven experienced transient viral load “blips”). The one individual with detectable HIV RNA was described as “0% adherent” due to lack of access to the drug. All patients experienced continued CD4 cell recovery, and no significant toxicity or drug resistance was observed.

Researchers also presented data from the MONARK trial, an ongoing 96-week open-label study in Europe (*abstract PL13.3*). In this trial, 83 treatment-naïve participants were randomly assigned to receive lopinavir/ritonavir monotherapy, while 53 took standard triple-combination therapy using lopinavir/ritonavir plus ATZ/3TC. After 48 weeks, virological suppression was similar in both arms, though those receiving monotherapy had more episodes of low-level viremia. At week 48, participants in the monotherapy arm reported fewer symptoms and improved overall health. The investigators concluded that “patients’ quality of life, estimated by the number of self-reported side effects and perception of global health, was better with lopinavir/ritonavir monotherapy when compared with a triple regimen of lopinavir/ritonavir plus AZT/3TC.”

In related news, ACTG 5201 investigators reported results from a study of atazanavir monotherapy in the August 16, 2006, *Journal of the American Medical Association*. In this open-label, multicenter trial, 34 patients on HAART who had maintained virological suppression for at least 48 weeks on their first PI-based regimen

switched to once-daily ritonavir-boosted atazanavir at study entry, then discontinued their NRTI backbone drugs after six weeks; all but one completed 24 weeks of therapy. At week 24, 31 participants (91%) had continued HIV suppression, while three (9%) experienced virological rebound. CD4 cell counts remained stable. Plasma atazanavir concentrations at the time of treatment failure were low or undetectable in two of these patients, but resistance testing did not identify PI-resistance mutations. No participants discontinued monotherapy due to adverse events, and there were no significant changes in blood lipid levels. “These preliminary data suggest that simplified maintenance therapy with atazanavir/ritonavir alone may be efficacious for maintaining virologic suppression in carefully selected patients with HIV infection,” the authors wrote.

BEST OUTCOMES WITH NNRTIS OR BOOSTED PIS

A decade after the advent of HAART, there remains some uncertainty about which are the optimal combination antiretroviral regimens for individuals starting treatment for the first time. To explore this issue, John Bartlett, MD, and colleagues have conducted periodic meta-analyses of data from studies of various regimens, culled from medical journals and conference abstracts. The latest update, published in the October 24, 2006 issue of *AIDS*, included 53 trials—with a total of 14,264 treatment-naïve participants—comparing triple-combination regimens comprised of a dual-NRTI backbone plus either a third NRTI, an NNRTI, or a boosted or unboosted PI.

Overall, more than half the subjects (55%) achieved HIV RNA levels below 50 copies/mL after 48 weeks of therapy; this percentage increased in studies with later publication dates, indicating that treatment has improved over time. Significantly more patients receiving NNRTI-based or boosted PI-based regimens achieved undetectable viral loads (64% for each), compared with those receiving triple-NRTI regimens (54%) or unboosted PIs (43%). In addition, CD4 cell count increases were significantly greater among patients receiving boosted PIs (200 cells/mm³), compared with unboosted PIs (179 cells/mm³), NNRTIs (173 cells/mm³), or triple-NRTI regimens (161 cells/mm³). While good adherence is known to promote better outcomes, a regimen’s convenience—as measured by “pill burden”—was not a significant predictor of undetectable viral load. The authors concluded that “NNRTI and boosted PI-containing regimens offer superior virologic suppression over 48 weeks, supporting existing guidelines for the choice of initial antiretroviral therapy.”

Beyond surrogate markers of disease progression such as HIV viral load and CD4 cell count, it is useful to also look at actual clinical end-points, such as the development of AIDS-related illnesses or death. As reported in the September 1, 2006, *Journal of Infectious Diseases*, researchers with the Antiretroviral Therapy Cohort Collaboration examined clinical disease progression in 12 European and North American cohort studies conducted between 1996 and 2003.

These studies included a total of 17,666 treatment-naïve participants taking regimens containing efavirenz, nevirapine (Viramune), indinavir (Crixivan), nelfinavir, full-dose ritonavir, unboosted saquinavir, ritonavir-boosted PIs, or triple-NRTI combinations including abacavir (Ziagen). Overall, 1617 new AIDS-related events and 895 deaths occurred. Patients taking efavirenz had a lower risk of progression to AIDS or death compared with those receiving nevirapine, full-dose ritonavir, or ritonavir-boosted PIs. Individuals starting therapy with nelfinavir, unboosted saquinavir, or abacavir had a risk of AIDS progression or death similar to that of patients starting with efavirenz—although these options are no longer considered preferred choices for initial therapy (see previous news item on DHHS treatment guidelines). However, regimen-based differences in mortality were small, and rates were much lower than those observed during the pre-HAART era. While long-term data are not yet available for second-generation antiretroviral drugs, this study illustrates the importance of following patients over the long term to assess ultimate outcomes.

ADHERENCE TO NNRTIS

Experts often say that individuals must achieve at least 95% adherence to realize the full benefits of antiretroviral therapy—a threshold largely derived from studies in which patients used unboosted PIs. But a study by David Bangsberg, MD, published in the October 2006 issue of *Clinical Infectious Diseases*, suggests that a lower adherence level may be adequate for patients taking NNRTIs. Researchers assessed the relationship between viral load suppression and adherence in 110 HIV positive participants enrolled in the San Francisco Research on Access to Care in the Homeless (REACH) study between July 1996 and April 2000; 56 took PI-based regimens (mostly unboosted), while 54 received NNRTI-based regimens.

After a mean follow-up period of nine months, a majority of participants in the NNRTI group achieved undetectable viral loads if they took between 54% and 100% of their prescribed medication. In the PI group, only patients who maintained at least 73% adherence achieved undetectable HIV RNA. Overall, the rate of virological suppression was significantly higher in the NNRTI group,

especially among subjects who achieved 54%–73% adherence. “Although perfect adherence is an important goal,” Bangsberg concluded, “viral suppression is possible with moderate adherence to potent regimens.”

In an accompanying editorial, Roy Gulick, MD, explained that the greater “forgiveness” of NNRTIs may be due to several factors, including the drugs’ inherent potency and their convenience, tolerability, and long plasma half-lives. However, he noted that many participants in Bangsberg’s study were taking unboosted first-generation PIs such as indinavir or nelfinavir, and suggested that second-generation boosted PIs—such as lopinavir/ritonavir or fosamprenavir—would likely offer “forgiveness” as well.

BOOSTED FOSAMPRENAVIR WORKS AS WELL AS LOPINAVIR/RITONAVIR

As noted above, the latest revision to the DHHS HIV treatment guidelines added ritonavir-boosted fosamprenavir to the list of preferred components of first-line antiretroviral regimens. This change was based in part on recent data showing that fosamprenavir worked as well as lopinavir/ritonavir in treatment-naïve patients.

The open-label, Phase IIIb KLEAN study included 878 antiretroviral-naïve participants with viral loads of at least 1000 copies/mL who were randomly assigned to receive either fosamprenavir/ritonavir (700 mg/100 mg twice daily) or lopinavir/ritonavir (400 mg/100 mg twice daily), both with fixed-dose abacavir/3TC (Epzicom). Data from KLEAN were presented at both the International AIDS Conference (*abstract THLB0205*) and at ICAAC (*abstract H-1056*), and were published in the August 5, 2006, issue of *The Lancet*.

At week 48, fosamprenavir/ritonavir was shown to be non-inferior to lopinavir/ritonavir using a metric known as TLOVR (Time to Loss of Virological Response). Similar proportions of patients in the two arms achieved HIV RNA levels below 400 copies/mL (73% vs 71%, respectively) and below 50 copies/mL (66% vs 65%, respectively). Median CD4 cell increases were similar in the two arms (176 vs 191 cells/mm³, respectively), as were blood lipid levels and rates of treatment discontinuation due to adverse events (12% vs 10%, respectively). The researchers concluded that “fosamprenavir/ritonavir twice daily in treatment-naïve patients provides similar antiviral efficacy, safety, tolerability, and emergence of resistance as lopinavir/ritonavir, each in combination with abacavir/[3TC].”

BOOSTED SAQUINAVIR APPEARS AS EFFECTIVE AS LOPINAVIR/RITONAVIR

Researchers presented interim data from another head-to-head PI comparison at the Glasgow meeting (*abstract*

PL2.5), suggesting that boosted saquinavir measures up to the newer lopinavir/ritonavir. In the Phase IIIb GEMINI study, 337 treatment-naïve participants were randomly assigned to receive either saquinavir/ritonavir (500 mg/100 mg twice daily) or lopinavir/ritonavir (600 mg/100 mg twice daily), both with fixed-dose tenofovir/emtricitabine (Truvada). In a 24-week intent-to-treat analysis of data from the first 150 subjects, similar proportions in the saquinavir/ritonavir and lopinavir/ritonavir arms achieved viral loads below 400 copies/mL (80.6% vs 83.6%, respectively) and below 50 copies/mL (69.4% vs 75.3%, respectively). Here, too, CD4 cell count increases and discontinuation rates (22%) were similar in both groups. However, significantly more participants in the lopinavir/ritonavir arm experienced elevated total cholesterol and triglyceride levels, contributing to a higher overall rate of Grade 2–4 adverse events (58% vs 48%). The GEMINI study will continue through 48 weeks.

ONCE- VS TWICE-DAILY LOPINAVIR/RITONAVIR

Simplicity and convenience—which contribute to good adherence—are important treatment considerations along with antiviral potency. In the October 1, 2006, *JAIDS*, researchers reported on a study of the safety and efficacy of once-daily versus twice-daily lopinavir/ritonavir. In this randomized, open-label trial, 190 antiretroviral-naïve participants with viral loads greater than 1000 copies/mL were randomly assigned to receive lopinavir/ritonavir at doses of either 800 mg/200 mg once daily or 400 mg/100 mg twice daily, in combination with once-daily tenofovir plus emtricitabine. After 48 weeks, virological response rates were similar in the two arms; in an intent-to-treat analysis, 70% of patients taking once-daily lopinavir/ritonavir and 64% in the twice-daily arm achieved HIV RNA levels below 50 copies/mL. Mean increases in CD4 count were also similar. Diarrhea—the most frequently reported side effect—was more common in the once-daily arm (16% vs 5%), but more participants in the twice-daily arm discontinued therapy prematurely (29% vs 20%). Once-daily lopinavir/ritonavir is already approved for treatment-naïve individuals, but twice-daily dosing is still recommended for treatment-experienced patients.

VIRAL LOAD DOES NOT PREDICT CD4 CELL DECLINE

In a majority of individuals, CD4 cell counts decrease as viral load increases over the course of HIV disease progression. A study published in the September 27, 2006, *Journal of the American Medical Association*, however, showed that this is not always the case.

Researchers analyzed data collected between May 1984 and August 2004 from 1289 patients followed at four U.S. sites, and 1512 participants in the San Francisco REACH homeless cohort and the Multicenter AIDS Cohort Study. Participants were not treated during the observation period (six months or longer). Overall, higher HIV RNA levels were associated with greater CD4 cell declines, ranging from 20 cells/mm³ in people with viral loads of 500 copies/mL or less, to 78 cells/mm³ in those with more than 40,000 copies/mL. Despite this broad trend, CD4 counts varied widely among individuals in a manner that was not predicted by viral load, and only 4%–6% of the variability in CD4 cell decline could be attributed to viral load changes. “Presenting HIV RNA level predicts the rate of CD4 cell decline only minimally in untreated persons,” the authors concluded. “Other factors, as yet undefined, likely drive CD4 cell losses in HIV infection.”

In an accompanying editorial, Keith Henry, MD, Pablo Tebas, MD, and Clifford Lane, MD, suggested that “measurements of viral load alone should have less of a role in driving decisions on when to start antiretroviral therapy for an individual patient,” since “initial viral load levels cannot predict how rapidly the disease will progress.”

Similarly, decreases in viral load do not always correlate with CD4 cell increases after starting HAART. At ICAAC, Mona Loutfy, MD, reported that patients who do not attain CD4 cell counts above 200 cells/mm³ may experience HIV disease progression despite complete virological suppression (*abstract H-1403*). The researchers studied a cohort of 299 antiretroviral-naïve participants with baseline CD4 counts below 200 cells/mm³ who initiated combination antiretroviral therapy between August 1996 and September 2003. While all subjects achieved viral loads below 50 copies/mL within one year of starting treatment, 97 (32.4%) did not attain CD4 counts of at least 200 cells/mm³. Ten such patients (10.3%) experienced clinical events, compared with 17 (8.4%) who did achieve higher CD4 counts. After one year on HAART, the respective rates of clinical events were 4.1% and 2.5%. “HIV-infected patients on combination antiretroviral therapy who achieve complete viral suppression but fail to attain CD4 [counts] greater than or equal to 200 cells/mm³ have increased clinical events within the first year of combination antiretroviral therapy,” the researchers concluded. If the CD4 count did not rise to 200 cell/mm³ or higher after one year, “there remained an increased risk of clinical events thereafter.” These results illustrate that while viral load is a useful indicator of how well HAART suppresses HIV replication, CD4 count remains the key measure of immune function.

Participants in a lifestyle modification program experienced significant decreases in waist circumference, systolic blood pressure, blood glucose, and lipodystrophy, while cardio-respiratory fitness improved.

DIABETES IN THE D:A:D STUDY

Studies have produced conflicting data about the occurrence of diabetes mellitus in people with HIV; several have observed higher rates among HIV positive individuals, possibly associated with use of antiretroviral therapy, especially PIs.

At the Glasgow meeting, researchers presented the latest results from D:A:D (Data Collection on Adverse Effects of Antiretroviral Drugs), an international observational study looking at complications of antiretroviral therapy over time in more than 33,389 participants (*abstract PL9.5*). They collected data about pre-existing and new cases of diabetes, and analyzed the relationship with antiretroviral drug exposure. A total of 952 participants (2.7%) had diabetes at study entry, and 745 of the remaining subjects developed new-onset diabetes over a follow-up period of six years (5.72 cases per 1000 person-years). Overall, the risk of developing diabetes rose by 6% for every year on antiretroviral therapy. But the rate doubled among patients exposed to d4T (Zerit), rising from about four to more than eight cases per 100 person-years. Use of ddI (Videx) and AZT (Retrovir) were also significantly associated with a higher risk of diabetes. PI use was not associated with an increase in the risk of diabetes in this study, and ritonavir was actually linked with a small but significant decrease. This finding remains unexplained, since new-onset diabetes was significantly associated with elevated total cholesterol and triglyceride levels, decreased high-density lipoprotein (HDL or “good”) cholesterol, and lipodystrophy, which are recognized side effects of some PIs.

BODY SHAPE CHANGES IN HIV POSITIVE MEN

Although HIV positive people on highly active antiretroviral therapy (HAART) frequently report body shape changes, comparisons with HIV negative individuals are necessary to determine which changes are potentially related to HIV infection or its treatment, and which are due to normal aging.

As reported in the November 1, 2006, *JAIDS*, researchers analyzed body shape changes among 661 HIV positive and 392 HIV negative men enrolled in the Multicenter AIDS Cohort Study, comparing body mass index (BMI) and waist, hip, thigh, and arm circumference at semiannual visits between 1999 and 2003. During the observation period, mean BMI increased significantly among the HIV negative men, but did not change in HIV positive men. Mean waist and hip circumference increased significantly in both groups, but rose more slowly in the 488 HIV positive subjects taking HAART, yielding a more

rapid increase in the waist-to-hip ratio in the treated HIV positive men. These results suggest that the abdominal fat gain reported by many HIV positive men on HAART may in fact be associated with aging rather than antiretroviral therapy, and may appear more pronounced due to changing waist and hip proportions.

MANAGEMENT OF METABOLIC COMPLICATIONS

Several recent journal articles and conference reports have contributed to the growing body of research on management of metabolic complications in people receiving antiretroviral therapy. A group of HIV/AIDS experts provided an overview of this topic in the September 1, 2006, issue of *Clinical Infectious Diseases*. “Changes in fat distribution, dyslipidemia, disordered glucose metabolism, and lactic acidosis have emerged as significant challenges to the treatment of HIV infection,” they wrote. “Metabolic complications of HIV infection and its therapies are common and may compromise antiretroviral tolerability, adherence, and, ultimately, treatment success. The development of conditions that alter body shape, threaten general well-being, and require treatment with additional medications can discourage even the most motivated patient.”

In a study described in the September 11, 2006, issue of *AIDS*, researchers assessed whether lifestyle modification could improve manifestations of the metabolic syndrome, including increased waist circumference, elevated blood pressure, elevated blood glucose, and abnormal blood lipid profiles. In this study, 34 HIV positive participants were randomly assigned to an intensive six-month lifestyle modification program or to a control group with no intervention. The program included weekly one-on-one counseling sessions with a registered dietician, and involved reducing total and saturated fat in the diet, adding omega-3 fatty acids and fiber, and increasing physical activity to at least three times per week at moderate intensity. Compared with the control group, participants in the lifestyle modification program experienced significant decreases in waist circumference, systolic blood pressure, blood glucose, and lipodystrophy, while cardio-respiratory fitness improved. However, cholesterol and triglyceride levels did not change. “These data demonstrate that intensive lifestyle modification significantly improved important cardiovascular risk indices in HIV-infected patients with the metabolic syndrome,” the authors concluded.

ATAZANAVIR LOWERS LIPID LEVELS

If lifestyle modification is not enough to control lipid abnormalities, another option is switching to the newer PI atazanavir, which causes less blood fat elevation than

other drugs in its class. At the Toronto conference, researchers reported data from a sub-study of the SWAN trial (*abstract THPE0123*), in which 153 participants with HIV RNA levels below 50 copies/mL were randomly assigned to remain on lopinavir/ritonavir or switch to once-daily unboosted atazanavir, while continuing the same background NRTIs. At week 48, rates of virological rebound and CD4 changes were similar in the two groups, but lipid parameters improved in the atazanavir switch arm; 4% of subjects in the atazanavir arm had elevated non-HDL cholesterol, compared with 17% in the lopinavir/ritonavir arm, and those in the atazanavir arm were less likely to need lipid-lowering medications (8% vs 21%). Another study (*abstract CDB0712*) found that lipid level changes in clinical practice were similar regardless of whether patients used boosted or unboosted atazanavir.

At the Glasgow meeting, researchers presented data from three analyses comparing the impact of atazanavir/ritonavir, fosamprenavir/ritonavir, and lopinavir/ritonavir on lipid profiles in patients matched for baseline cholesterol and triglyceride levels (*abstract P127*). They found that boosted fosamprenavir and lopinavir raised the total cholesterol level by similar amounts (about 10–15 mg/dL), while it fell by about 10 mg/dL in the boosted atazanavir arms. Likewise, fosamprenavir/ritonavir and lopinavir/ritonavir both increased triglyceride levels (by about 20 mg/dL and 30–40 mg/dL, respectively), while levels decreased (by 4–12 mg/dL) in the atazanavir/ritonavir arms. With all three drugs, HDL cholesterol increased by a similar amount (about 5 mg/dL).

TREATMENT OF FAT LOSS

Fat loss—both HIV-related wasting and peripheral lipoatrophy associated with certain NRTIs—represents a significant problem for many people with HIV/AIDS. Two recent studies assessed a variety of treatments for body fat changes.

The HALT (HIV-Associated Lipoatrophy Treatment) study, reported at ICAAC (*abstract H-1897*), enrolled 60 HIV positive men with lipoatrophy who were randomly assigned to one of five treatment arms: pravastatin (Pravachol), rosiglitazone (Avandia), or pravastatin plus rosiglitazone (all for 48 weeks), recombinant human growth hormone (Serostim), or growth hormone plus rosiglitazone (both for 12 weeks). Neither pravastatin nor rosiglitazone, alone or in combination, affected body composition or clinical parameters. Growth hormone produced significant reductions in visceral abdominal and trunk fat as assessed by CT scans (by 26% and 27%, respectively), and increased trunk and limb lean body mass as assessed by DEXA (by 10% and 12%, respectively). However, the effects were almost completely reversed within 12 weeks

after treatment discontinuation. Adding rosiglitazone alleviated the insulin resistance that occurred with growth hormone alone. Total and low-density lipoprotein (LDL or “bad”) cholesterol levels fell in the pravastatin arm but were unaffected by the other therapies. “Neither pravastatin nor rosiglitazone are effective therapies for body composition changes,” the researchers concluded. “[Growth hormone] is effective at reducing visceral fat and its deleterious effects on insulin resistance can be reduced by co-administration of rosiglitazone, but its effects are short-lived.”

As reported in the November 7, 2006, electronic edition of the *Journal of Clinical Endocrinology and Metabolism*, researchers assessed whether megestrol acetate (Megace) plus testosterone could improve lean body mass in patients with wasting; megestrol acetate promotes weight gain, but much of the added weight is in the form of fat. This randomized, double-blind trial, conducted at 14 ACTG units, included 79 HIV positive men with at least 5% weight loss or a BMI less than 20 kg/m². Participants were randomly assigned to receive megestrol acetate plus either testosterone enanthate or placebo biweekly for 12 weeks. Both the testosterone and placebo groups experienced increases in total body weight, lean body mass, and fat; there were no significant differences between the two arms in the extent or composition of weight gain. However, the addition of testosterone preserved sexual functioning, which decreased in the megestrol/placebo arm.

Taken together, these studies indicate that current therapies for weight loss and body shape changes in people with HIV leave much to be desired. As such, the best approach may be to prevent these problems in the first place, for example by switching away from thymidine analog NRTIs that can cause lipoatrophy.

LIVER TOXICITY DUE TO ANTIRETROVIRAL THERAPY

Liver toxicity is a potentially serious side effect associated with antiretroviral therapy; though usually mild to moderate, in rare cases it can lead to liver failure and death. In the November 1, 2006, *JAIDS*, researchers reported on the largest analysis to date of predictors of serious liver toxicity in patients on antiretroviral therapy, comprising 8851 participants enrolled in 16 AIDS Clinical Trials Group (ACTG) studies between October 1989 and June 1999. Severe hepatotoxicity—defined as aminotransferase levels more than 5 times or total bilirubin levels more than 2.5 times the upper limit of normal—occurred in 824 individuals (9.3%) during the first year of therapy: 613 (6.92%) during the first six months, and an additional 211 (2.38%)

Two studies presented at ICAAC found that female gender and higher CD4 counts did not increase the risk of liver problems.

during the next six months. A total of 79 deaths (0.9%) were attributed to liver-related illness. Baseline alanine aminotransferase (ALT) elevation, use of other hepatotoxic medications besides antiretroviral drugs, low platelet count, impaired kidney function, coinfection with hepatitis C virus (HCV), and use of ddI, d4T, or nevirapine were significant risk factors for severe liver toxicity.

The authors emphasized the importance of a thorough work-up, including liver function tests and HCV status, before starting antiretroviral therapy. While most cases of serious liver toxicity occurred soon after starting therapy, some cases still emerged after six months, illustrating the importance of continued monitoring of liver function during antiretroviral treatment.

RISK FACTORS FOR NEVIRAPINE LIVER TOXICITY

Previous studies and reports of “real world” cases indicate that women with CD4 cell counts above 250 cells/mm³ and men with levels above 400 cells/mm³ are more likely to have hepatotoxicity due to nevirapine. Two studies presented at ICAAC, however, found that female gender and higher CD4 counts did not increase the risk of liver problems.

German researchers reported on a retrospective review of Grade 3–4 liver toxicity (ALT levels greater than 5 times the upper limit of normal) in 507 patients who started nevirapine between 1996 and 2005 (*abstract H-1063*). In terms of potential risk factors, 22% were women, 17% had baseline elevated ALT, and 13% were coinfecting with hepatitis B or C; 40% of women had CD4 counts greater than 250 cells/mm³ and 27% of men had more than 400 cells/mm³. After a mean observation period of 21 months, 4.6% of patients overall experienced liver toxicity, and 7.5% discontinued therapy for this reason. Among women with CD4 counts above 250 cells/mm³, 5.6% experienced Grade 3–4 ALT elevations, versus 6.3% of women with lower CD4 counts. Among men with CD4 counts above and below 400 cells/mm³, the rates were 6.5% and 3.4%, respectively. In a multivariate analysis, however, the only independent risk factors for serious liver toxicity were baseline ALT elevation and hepatitis B or C coinfection; neither gender nor CD4 count were significantly associated with an increased risk of liver toxicity.

Likewise, Spanish researchers conducted a meta-analysis of four randomized studies in which a total of 410 individuals with virological suppression switched to regimens containing nevirapine (*abstract H-1064*); 133 patients were classified as having “low” CD4 cell counts (below 250 cells/mm³ for women or below 400 cells/mm³ for men), while 277 had “high” levels. The risk of liver toxicity was 2% in the low CD4 cell count group (women

and men combined), compared with 4% in the high CD4 group, but the difference did not reach statistical significance. The only factor significantly associated with an increased risk of hepatotoxicity was elevated baseline aminotransferase levels. However, two patients (1%) in the high CD4 cell group, but none in the low CD4 group, developed symptomatic hepatitis.

During a discussion of these two studies, speakers noted that thousands of patients used nevirapine before the effect of gender and CD4 count on liver toxicity became apparent. It was not identified in early clinical trials that led to the drug’s approval, and the recent studies (which included about 900 total subjects) may have been too small to show this pattern.

In related news, two studies published in the September 15, 2006, issue of *Clinical Infectious Diseases* suggested that genetic testing may help predict who will experience serious liver toxicity when using nevirapine. Both showed that a specific genetic variation—the MDR1 3435 C-to-T polymorphism—was associated with a decreased risk of hepatotoxicity in patients taking NNRTIs. *MDR1*, the multidrug-resistance gene, encodes P-glycoprotein, a protein that expels drugs from cells. A test for the *MDR1* variation is not yet clinically available, but in the future, genetic assays such as this may help health-care providers tailor antiretroviral regimens to specific individuals.

NATURAL CONCEPTION USUALLY SAFE FOR SERODISCORDANT COUPLES

Use of AZT and other antiretroviral agents has reduced the risk of mother-to-child HIV transmission to less than 2%, but HIV positive individuals can potentially transmit the virus to an HIV negative partner while trying to conceive. Assisted reproduction methods such as artificial insemination, *in vitro* fertilization, and sperm washing reduce the risk of sexual transmission, but these techniques are cumbersome and expensive.

As reported in the November 1, 2006, *JAIDS*, Spanish researchers reviewed medical records of 62 HIV serodiscordant couples who achieved natural pregnancies without medical assistance; in 22 couples, the woman was HIV positive, while the man was positive in 40. At the time of conception, all HIV positive partners were receiving HAART and had undetectable viral load, and all of the HIV positive women had undetectable HIV RNA during pregnancy and at the time of delivery. Overall, 76 natural pregnancies occurred and 68 children were born. There were no recorded cases of HIV seroconversion in any of the uninfected partners, although one woman transmitted HIV to her baby despite prophylactic therapy. The authors concluded that “serodiscordant couples attaining natural pregnancy are

exposed to a negligible risk of sexual transmission of HIV when the infected partner presents with complete suppression of plasma viremia while receiving HAART.” However, to minimize the risk of sexual transmission while maximizing the odds of pregnancy, they recommended that unprotected intercourse should be limited to the fertile days of a woman’s menstrual cycle.

**HIGHER DOSES OF LOPINAVIR/
RITONAVIR DURING PREGNANCY**

Pregnancy can affect the processing and pharmacokinetics of antiretroviral drugs, potentially leading to suboptimal concentrations, which can have a detrimental effect on the woman’s health and increase the risk of mother-to-child HIV transmission.

As reported in the October 3, 2006, issue of *AIDS*, researchers with the PACTG 1026s study conducted an analysis of lopinavir/ritonavir pharmacokinetics during pregnancy; about two-thirds of the women were also taking AZT/3TC. Based on intensive steady-state pharmacokinetic analyses of lopinavir and ritonavir levels, they found that 14 of 17 pregnant women (82%) and three of 12 postpartum women (25%) did not achieve the target lopinavir levels associated with optimal efficacy. After delivery, however, lopinavir levels returned to the target level in most women, doubling the concentrations observed during late pregnancy. Since pregnant women had lopinavir levels about half those seen in non-pregnant adults, the researchers recommended that the pharmacokinetics, safety, and effectiveness of increased lopinavir/ritonavir dosing during the third trimester of pregnancy should be investigated.

**NATURAL HEALTH PRODUCTS
AND ANTIRETROVIRAL DRUGS**

A large proportion of people with HIV/AIDS (70% in one study) use natural health products in addition to HAART. But such use can present a problem, since some herbal remedies and nutritional supplements can interact with antiretroviral drugs. Researchers from Johns Hopkins published a review of known pharmacokinetic and pharmacodynamic interactions between natural health products and antiretroviral agents in the October 15, 2006, issue of *Clinical Infectious Diseases*.

“Many natural health products are complex mixtures and are likely to contain organic compounds that may induce and/or inhibit drug metabolizing enzymes and drug transporters,” they wrote. Inducers of cytochrome P450 enzymes can lead to faster drug processing, subtherapeutic concentrations, and reduced efficacy, while enzyme inhibitors can result in higher drug concentrations and

worse toxicity. Plant-based products shown to influence these enzymes in laboratory or clinical studies include St. John’s wort, grapefruit juice, garlic, milk thistle, goldenseal, and echinacea. Other herbal compounds influence the activity of the P-glycoprotein transporter, which eliminates drugs from the body. On the other hand, fish oil supplements may improve elevated blood fat levels associated with some antiretroviral drugs.

“Data from published studies are often suboptimal, contradictory, and outdated, and new studies are urgently needed,” the authors wrote. “In the meantime, caution should be exercised and clinicians should always be vigilant to the possibility of interactions between natural health products and antiretroviral drugs in their patients.”

Individuals on HAART should let their health-care providers know about any products they are taking, including prescription and over-the-counter medications, alternative/complementary remedies, and street drugs, since these may interact with antiretroviral therapy.

Liz Highleyman is a freelance medical writer and editor based in San Francisco.



Blast from the Past

Check out these articles from past issues of *BETA* to learn more about medical research and HIV health:

“A Guide to Clinical Trials Part I: Understanding Clinical Studies”
(Summer 2005)

“A Guide to Clinical Trials Part II: Interpreting Medical Research”
(Winter 2006)

“Overcoming Depression”
(Winter 2004)

“Sexually Transmitted Diseases and HIV-Related Risks”
(Autumn 2000)

“Monitoring Tests for People with HIV”
(Summer 2003)

These and other articles are available at www.sfaf.org/beta. Some are available in print; call 415-487-8060 or write to beta@sfaf.org or *BETA*, PO Box 426182, San Francisco, California 94142-6182.