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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/ndxlipoh.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_aasld/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-naïve, 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-naïve 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 Podzamczar, 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/mm³, compared with 200 cells/mm³ 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/mm³). 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/mm³ 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/mm³. 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/mm³ restarted in about seven months, compared with about 14 months for those with nadirs of 200–350 cells/mm³ and about 18 months for those with nadirs of 350–500 cells/mm³. No one with a CD4 nadir above 500 cells/mm³ 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/mm³, 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 were 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-naïve 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-naïve 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-naïve 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 naïve 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-naïve 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-naïve 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-naïve 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-naïve 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 anti-retroviral 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/mm³. 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/mm³ were as likely to survive as those who started with a CD4 cell count of 350 cells/mm³ 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/mm³. 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/mm³ 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 coinfecting 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 coinfecting 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 coinfecting 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 Kottlilil, MD, of the NIH (abstract V-1724) and colleagues reported that although only one of 11 coinfecting 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. Kottlilil 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 coinfecting 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 coinfecting subjects, liver fibrosis (scarring) appeared to progress more slowly in those receiving HAART compared with those not receiving anti-HIV treatment.

For HIV/HCV-coinfecting 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-coinfecting individuals. Analyzing a cohort of 285 coinfecting 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-naïve, 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-naïve 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 breastfeeding. 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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