

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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DRUG SAFETY

New Data Sound Death Knell for Long-Term Hormone Replacement Therapy

Now that the storm raised by new reports of the limited benefits and increased risks associated with hormone replacement therapy (HRT) in postmenopausal women has subsided, we can step back and ask what we have learned. On July 9, the directors of the Women's Health Initiative, the first and only large trial to compare the effects of HRT—conjugated estrogens and medroxyprogesterone (*Prempro*)—with placebo, sent letters to the study's 16,608 participants telling them to stop taking their assigned medication. The communication advised participants that after women in the study had taken the drugs for an average of 5.2 years, an interim analysis showed that the breast cancer risk exceeded the predefined boundary for safety [*JAMA* 2002;288:321-33].

The data indicated that if 10,000 women take the drugs for one year, 8 more would develop invasive breast cancer, compared with 10,000 women who were not taking the drug. That was not the only concern. An additional 7 women would have a myocardial infarction, 8 would have a stroke, and 18 would develop blood clots, including 8 who would also develop pulmonary embolism. Are there benefits? Yes, but modest ones. There would be 6 fewer colorectal cancers and 5 fewer hip fractures. While harm to an individual is small, overall, the drugs' risks exceed their benefits. The purpose of healthy women taking HRT long-term is to preserve health and prevent disease—the study shows the opposite is happening. Moreover, there are alternatives to HRT, such as the bisphosphonates and raloxifene, which reduce the risk of hip fractures, as well as well-proven treatments to reduce the risk of cardiovascular disease.

The reported results do not include data on 11,000 women who had had hysterectomies and were treated with conjugated estrogens (*Premarin*) alone. These women continue to be studied in the trial. Progestin is added to HRT only to prevent unopposed estrogen from increasing the risk of cancer of the uterine lining.

The trial did not address the benefits of using HRT for a short period to relieve symptoms of menopause—hot flashes, night sweats, and vaginal dryness. HRT is thought to be the most effective treatment for menopausal symptoms and the large majority of physicians who prescribe it initially do so for this reason. But most of them allow women to continue hormone replacement under the assumption that therapy will have a net health benefit, reducing heart attacks, now

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DRUG SAFETY (continued)

Long-Term Hormone Replacement Therapy (continued)

disproved, and decreasing the incidence of fractures. This approach is no longer tenable. If a woman requires HRT for menopausal symptoms, she can safely take it for two to three years, followed by withdrawal. If symptoms persist, the woman can again be prescribed HRT for an additional year. Beyond that, alternatives should be considered. Data suggest that women with heart disease should not receive HRT even short-term for menopausal symptoms.

For women with severe menopausal symptoms who refuse HRT, for those who have taken HRT for four years but continue to be discomfited by symptoms, and for those with a history of breast cancer, several alternatives have been proposed, but evidence supporting their use ranges from none to weak. For many years women have turned to dietary products containing soy or to soy supplements rich in plant estrogens. Food products that contain soy are probably safe but no solid evidence supports efficacy. The herb Black Cohosh has been used as has been the drug clonidine. Short-term controlled studies (4 to 5 weeks) with fluoxetine, ven-

lafaxine, paroxetine, or sertraline in a total of 151 women with menopausal symptoms reported significant reduction in hot flashes and amelioration of other symptoms.

The Women's Health Initiative tested only *Prempro*, the most widely used HRT. There are many other hormone replacement therapies on the market and a host of alternative remedies such as natural estrogens. Advocates of long-term HRT, sincere and unscrupulous ones alike, are touting other products containing human estrogen and progestin or plant hormones as safer than *Prempro*, but without a scintilla of evidence. There are also those who believe that a lower dose of *Prempro* retains its benefits and may eliminate its risks. Proponents of transdermal estrogen say that this method of delivery does not expose the liver to high concentrations of hormones during absorption from the gastrointestinal tract and is therefore safer. All we can say at this time is that if a product has estrogenic effects, it is likely to share at least some of the risks posed by *Prempro*. Only clinical trials will disprove this.

Oral Contraceptives and the Risk of Breast Cancer

Whether the use of oral contraceptives increase the risk of breast cancer later in life is uncertain. To clarify the matter, researchers conducted a population-based, case-control study to examine the use of oral contraceptives as a risk factor for breast cancer in women who were 35 to 64 years old [*N Engl J Med* 2002; 346:2025-32].

A total of 4575 women with breast cancer and 4683 controls were interviewed. The relative risk of breast cancer was 1.0 (95% CI, 0.8 to 1.3) for women currently using oral contraceptives and 0.9 (95% CI,

0.8 to 1.0) for those who had previously used them. Relative risk did not increase consistently with longer periods of use or with higher doses of estrogen. The results were similar among white and black women. Neither the use of oral contraceptives by women with a family history of breast cancer nor the initiation of oral contraceptive use at a young age was associated with an increased risk of breast cancer. The study provides further reassurance that the use of oral contraceptives, even for a long period, is not associated with an increased risk of breast cancer [*Ibid*, 2078-79].

Oral Contraceptives and the Risk of Thromboembolism After Surgery

A recent report in the *Prescriber's Letter* [2002;9:39] notes that both surgery and estrogen can increase the risk of thrombosis and that women taking oral contraceptives have a two to four times higher risk of thromboembolic complications after surgery. In light of this, physicians should advise women taking oral contraceptives to discontinue them four weeks before

major surgery or any prolonged immobilization and discuss alternative contraception. Oral contraceptives may be resumed in two weeks after ambulation. If stopping oral contraceptives before major surgery is not feasible, the newsletter recommends the use of heparin and compression stockings to help prevent deep vein thrombosis.

Lansoprazole Prevents Ulcer Recurrence in Patients on Low-Dose Aspirin

Patients taking low-dose aspirin for prevention of cardiovascular and cerebrovascular diseases have an increased risk of ulcer complications, and some should receive prophylactic treatment. An available option is the simultaneous use of proton-pump inhibitors. Since *Helicobacter pylori* infection is frequently found in patients with ulcer bleeding and is an important risk factor for peptic-ulcer, investigators compared the efficacy of eradication of *H. pylori* infection with that of eradication plus continuous therapy with a proton-pump inhibitor on ulcer recurrence [*N Engl J Med* 2002;346:2033-38].

They enrolled 123 patients who had ulcer complications after using low-dose aspirin continuously for more than one month and who had *H. pylori* infection. After the ulcer had healed and the infection was eradicated, the patients were randomly assigned to treatment

with lansoprazole 30 mg/day or placebo, in addition to aspirin 100 mg/day, for 12 months.

During follow-up, 9 of 61 patients in the placebo group (14.8%) as compared with 1 of 62 patients in the lansoprazole group (1.6%) had a recurrence of ulcer complications. Of these 10 relapsed patients, 4 had recurrent *H. pylori* infection and 2 had taken NSAIDs in addition to aspirin before the onset of complications.

The lead investigator told *Reuters Health* [28 June 2002] that he believes other proton-pump inhibitors are likely to work as well in preventing ulcer recurrence in patients who take aspirin. He also pointed out that because most patients who take low-dose aspirin will not develop ulcer complications, "it may not be wise to systematically prescribe a proton-pump inhibitor to all such patients to prevent only a few from developing ulcers."

New Labeling for Irinotecan Stresses Diarrhea Warnings

The FDA issued an alert highlighting a letter sent to healthcare professionals to inform them of changes in the prescribing information of irinotecan (*Camptosar*), which is used in combination with 5-fluorouracil and leucovorin as first-line treatment for metastatic colorectal cancer. The prescribing information has been updated to emphasize that patients with diarrhea should be carefully monitored and given appropriate therapies if they develop dehydration, ileus, fever, or severe neutropenia. This information is contained in a boxed warning. Patients with active diarrhea after their first

treatment should not receive subsequent chemotherapy until they show pretreatment bowel function for least 24 hours without the aid of antidiarrhea medication. If moderate to severe late diarrhea occurs, subsequent doses of irinotecan should be decreased within the current cycle. Both the bolus and infusion regimens for irinotecan combined with 5-FU and leucovorin remain approved as first-line therapy and starting doses and schedules for the regimens are unchanged [*Reuters Health*, 9 July 2002].

NEW DRUGS AND INDICATIONS

FDA Approves Long-Acting *Aranesp* for Anemia in Cancer Patients

Amgen announced that its second-generation erythropoietin, *Aranesp* (darbepoetin), initially approved for the treatment of anemia in kidney dialysis patients, has now received FDA approval for use in the treatment of anemia in cancer patients undergoing chemotherapy. *Aranesp* is administered less frequently than its competitor *Procrit*. Amgen will heavily promote this difference. There is no evidence at this time of differences in efficacy or safety [*Reuters Health*, 23 July 2002].

Approval of the new indication was supported by a study that assessed the outcomes of 297 lung cancer

patients with chemotherapy-related anemia who were randomly assigned to receive darbepoetin or placebo injections weekly for 12 weeks [*J Natl Cancer Inst* 2002;94:1211-20]. Compared with patients who received placebo, darbepoetin-treated patients required fewer blood transfusions and fewer units of blood. They were also more likely to experience hematopoietic response and less fatigue. Treatment did not induce anti-darbepoetin antibodies and the incidence of treatment-related side effects was similar in both groups. Additional studies are underway to determine if darbepoetin can be administered as infrequently as every two to three weeks [*Reuters Health*, 21 August 2002].

NEW DRUGS AND INDICATIONS (continued)

FDA Approves *Zelnorm* for Women with IBS

The FDA recently announced that it has approved *Zelnorm* (tegaserod) tablets for the short-term treatment of women with irritable bowel syndrome (IBS), a group that could number up to 3.7 million. Tegaserod is the first medication to be approved for the treatment of constipation-predominant IBS. In approving the drug, the FDA stressed that *Zelnorm* does not cure IBS or benefit those with diarrhea-predominant disease. But it has been shown to reduce constipation, bloating, and abdominal discomfort.

Tegaserod is a 5HT₄ partial agonist and appears to work by stimulating the peristaltic reflex. The most

common side effects in trials of the drug were headache and diarrhea. Diarrhea in most patients was mild and short-lived. *Zelnorm* has not been adequately evaluated in men with IBS. FDA critics objected to *Zelnorm*'s approval, citing its modest benefit and the availability of alternatives that may be no less effective.

In addition to limiting its use to women with constipation, the FDA also recommends that *Zelnorm* should be taken for only four to six weeks to start and, if effective, taken for an additional four to six weeks. There are no data to support continued use.

New Treatments for Actinic Keratoses

The Medical Letter recently reported on new treatments for actinic keratoses, including topical aminolevulinic acid, diclofenac gel, and imiquimod cream [Med Lett 2002;44:57-58]. Cryosurgery with liquid nitrogen is the most common technique used to destroy actinic keratoses. When lesions are too numerous, topical fluorouracil is applied for several weeks. Therapy with 5-FU is effective in more than 90% of

patients who can tolerate it and offers the advantage of treating clinically undetectable keratoses, but it can cause temporarily disfiguring erythema, blisters, and ulceration.

The FDA has approved a 20% solution of aminolevulinic acid (*Levulan Kerastick*), a porphyrin-based photosensitizer used with photoactivating blue light for

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CLINICAL PRACTICE

Safer Alternatives to *Accutane* for the Treatment of Acne

The Wall Street Journal Online [30 April 2002] reported that patients, parents, and physicians are increasingly worried about both documented and arguable side effects—depression and suicidal ideations among them—associated with the use of isotretinoin (*Accutane*) by adolescents with acne. These concerns have set off a search for less-toxic options. Although nothing works as well as *Accutane*, dermatologists report that alternative therapy may benefit up to 85% of sufferers.

A promising alternative to *Accutane* is tazarotene (*Tazorac*), a retinoid, like isotretinoin, formulated for once-daily topical use. The FDA approved *Tazorac* last fall. Related topical retinoid

products also useful for the treatment of acne are adapalene (*Differin*) and tretinoin (*Retin-A Micro*). Side effects of topical product are less serious than those encountered with *Accutane*, but locally applied agents can be highly irritating, causing redness, peeling, and burning. Like *Accutane*, they carry a risk of birth defects, so women who use them must avoid pregnancy.

In comparative studies, Allergan demonstrated that *Tazorac* was more effective against acne than *Retin-A Micro* or *Differin*, but produced significantly more local side effects. *Differin*, the mildest product, may be a better choice for patients with sensitive skin.

New Treatments for Actinic Keratoses (continued)

actinic keratoses of the face and scalp. Treatment is effective in about two-thirds of patients and has the advantage of a two-day course but commonly causes erythema and edema, and can cause erosions. The FDA has also approved a topical 3% gel containing the NSAID diclofenac (*Solaraze*). Twice-daily topical application leads to complete resolution of lesions in only one-third to one-half of patients but it is better tolerated than aminolevulinic acid; common side effects are dry skin, pruritus, erythema, and rash. Imiquimod

5% cream (*Aldara*), an immunostimulant previously approved for treatment of genital warts, has also been used to treat actinic keratoses.

The editors of *The Medical Letter* observed, “Imiquimod may prove to be worth trying, but data are minimal and it has not been approved for this indication. For small actinic keratoses that are not too numerous, liquid nitrogen or surgical curettage remains the treatment of choice.”

Neurontin Now Approved for Postherpetic Neuralgia

The FDA has officially sanctioned the already widespread use of *Neurontin* (gabapentin) for persistent neuropathic pain that occurs in about half of older patients after a bout with herpes zoster (shingles). Tricyclic antidepressants have long been used to treat postherpetic neuralgia but they can cause serious side

effects, especially in the elderly. Gabapentin appears to be as effective as tricyclics and is usually better tolerated. For patients with postherpetic neuralgia, the dose of gabapentin can be gradually increased up to 600 mg three times day, if needed [*Prescriber's Letter* 2002; 9:39-40].

Acetylcholinesterase Inhibitors for Vascular Dementia

Results from a second phase III trial of the acetylcholinesterase inhibitor *Aricept* (donepezil) in patients with vascular dementia show that it significantly improves cognition and global function compared with placebo, confirming the positive findings from the earlier study [*Scrip*, 26 April 2002]. Eisai and its marketing partner, Pfizer, plan to file both studies with regulatory

authorities to gain approval for the additional indication. *Aricept* is already widely available for the treatment of Alzheimer's disease, but the new indication could greatly extend its market.

The other acetylcholinesterase inhibitors—*Reminyl* (galantamine) and *Exelon* (rivastigmine)—are also
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CLINICAL PRACTICE (continued)

Updated NIH Consensus on Hepatitis C Treatment

The National Institutes of Health has issued a new consensus statement on the management of hepatitis C to take into account the introduction of new treatment options for the infection. The statement, developed by an independent panel of experts, updates the one issued in 1997. A four-fold increase in the number of people in the U.S. with chronic hepatitis C infection is projected over the next decade.

In developing the statement, panel members examined pivotal data for pegylated interferons, both *Peg-Intron* (peginterferon alfa-2b), which was approved last year, and *Pegasys* (peginter-

feron alfa-2a), which may be approved this year. They concluded that combination therapy with either of these products plus ribavirin gives the highest response rates in treatment-naive patients.

The report also highlights the side effects of combination therapy and widens the scope of patients eligible for therapy. “The side-effects for hepatitis C therapy are unpleasant and include influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms” [*Scrip*, 21 June 2002]. The statement adds, “Antidepressants, such as SSRIs, may be useful in the management of less severe depression.”

NEW DRUGS AND INDICATIONS (continued)

Acetylcholinesterase Inhibitors for Vascular Dementia (continued)

being investigated for use in vascular dementia. Both are in phase III trials. Positive results from a six-month phase III study of *Reminyl* in patients with vascular dementia or mixed dementia (vascular dementia and Alzheimer's) were published in *The Lancet* [2002; 359:1283-90]. Study investigators reported that galantamine showed a therapeutic effect on all key areas of

cognitive and noncognitive abilities in this group of patients. However, the author of an accompanying commentary criticized the way the results of the study were analyzed. He said the overall analysis failed to consider the outcomes in the Alzheimer's and vascular dementia group separately [*Ibid*, 1265-66].

DRUG EVALUATION

Antiinflammatory Drugs Not Effective in Established Alzheimer's Disease

Although interest is keen in the use of nonsteroidal antiinflammatory drugs for the prevention or amelioration of Alzheimer's disease, solid evidence supporting this strategy is lacking and a new report casts doubt on its merit. A presentation at the 8th International Conference on Alzheimer's Disease and Related Disorders described the randomization, and subsequent evaluation, of 351 patients with mild to moderate Alzheimer's disease to rofecoxib (*Vioxx*), naproxen, or placebo. Most patients in the study were also taking an acetylcholinesterase inhibitor.

At the end of one year, analysis showed cognitive decline in each group. The mean change in the

Alzheimer's Disease Assessment Scale (ADAS_{cog}) score was 5.69 for placebo, 5.77 for naproxen, and 7.63 for rofecoxib. Differences were not statistically significant, but a trend was observed toward greater cognitive decline in the rofecoxib group than in the other groups. The incidence of serious adverse events in both the naproxen and rofecoxib arms was higher than in the placebo arm. The principal investigator concluded, "The inflammatory hypothesis is an intriguing but unproven strategy." He concluded, "There is insufficient information to support recommendations to use antiinflammatory agents to treat Alzheimer's disease at this time" [*Reuters Health*, 25 July 2002].

CLINICAL PRACTICE (continued)

Anticoagulants and Antiplatelet Agents in Acute Ischemic Stroke

The Report of the Joint Stroke Guidelines Development Committee of the American Academy of Neurology and the American Stroke Association examines the published evidence relevant to the effects of anticoagulants and antiplatelet agents on acute ischemic stroke mortality, morbidity, and recurrence rates [*Neurology* 2002;59:19-22]. Considerable evidence supports the use of certain antithrombotic drugs in stroke prevention, but data in support of the use of these agents to treat acute ischemic stroke is limited. The report recommends:

- Patients presenting within 48 hours of symptoms onset should be given aspirin

(160 to 325 mg/day) to reduce stroke mortality and decrease morbidity, provided contraindications are absent and the patient is not to receive thrombolytic therapy. Data are insufficient to recommend the use of any other antiplatelet agent in this setting.

- Subcutaneous heparin and low molecular weight (LMW) heparins may be considered for deep-vein thrombosis prophylaxis in at-risk patients with acute ischemic stroke.
- Fixed-dose heparin appears to reduce early recurrent ischemic stroke but this benefit is

Lamivudine in Children with Chronic Hepatitis B

Chronic hepatitis B affects about 5% of the world's population. Those who become infected as children are at highest risk for chronic infection, cirrhosis, and hepatocellular carcinoma. Therapeutic options for adults with chronic hepatitis B include lamivudine and interferon alfa. Now, the International Pediatric Lamivudine Investigators Group have reported on the safety and efficacy of lamivudine treatment in infected children [*N Engl J Med* 2002;346:1706-13].

The investigators determined that a virologic response occurred in 23% of children who received a one-year course of lamivudine and 13% of those who received placebo. Treatment was well tolerated, but lamivudine-resistant hepatitis B virus mutants were detected in 19% of children in the lamivudine group.

The baseline aminotransferase level was the strongest predictor of response.

Lamivudine is given orally. A perspective on the study says its availability has increased enthusiasm regarding the use of therapy for chronic hepatitis B, but the severity of liver disease and the likelihood of a response must be taken into account before treatment is initiated. Clinical trials indicate that interferon alfa and lamivudine have similar efficacy. The main advantage of interferon alfa is the absence of resistance; the disadvantages are its costs and side effects. "Lamivudine is less expensive and is well tolerated, but the duration of the response and the long-term clinical significance of the resistant mutants, particularly in children, are uncertain" [*Ibid*, 1682-83].

Vitamin E Supplements and Macular Degeneration

Age related macular degeneration (AMD) is the leading cause of blindness and loss of vision in developed countries. There is no effective method of prevention. Researchers undertook a prospective randomized controlled trial to examine whether a high-dose supplement of vitamin E influenced the development of AMD. Nearly 1200 healthy volunteers between 55 and 80 years received vitamin E or placebo daily for four years. The incidence of early AMD was 8.6% in

those receiving vitamin E compared with 8.1% in those who received placebo. The incidence of late disease was slightly higher in the vitamin E group than in the placebo group but the difference was not significant. The investigators concluded that daily vitamin E supplement does not prevent the development or progression of early or later stages of AMD [*BMJ* 2002;325:11-14].

CLINICAL PRACTICE (continued)

Anticoagulants & Antiplatelets in Acute Ischemic Stroke (continued)

negated by a concomitant increase in hemorrhage.

- Dose-adjusted heparin is not recommended to reduce morbidity, mortality, or early recurrent stroke in patients with acute stroke. High-dose LMW heparins have not been associated with either benefit or harm and are therefore not recommended.

The chair of the development committee said that evidence shows a slight benefit to giving aspirin early in stroke. "It's not a powerful effect

but the benefit appear to be real" [*Lancet* 2002;360:232]. An independent expert observed that the effects of aspirin would not be noticed by individual patients or by physicians in their own practices because the benefit is modest. "But the use of aspirin in this setting makes sense from a public health point of view since stroke is common and the treatment is inexpensive" [*Ibid*].

DRUG EVALUATION (continued)

Lopinavir/Ritonavir Better Choice for Initial Therapy of HIV Infection

The dual protease-inhibitor formulation of lopinavir and ritonavir (*Kaletra*) demonstrates better antiviral activity than a regimen that contains nelfinavir (*Viracept*). This is the conclusion of a study assessing the outcomes of 653 HIV-infected adults who were randomly assigned to receive lopinavir/ritonavir twice daily or nelfinavir three times daily as initial treatment. All patients also received stavudine and lamivudine [*N Engl J Med* 2002;346:2039-46].

At week 48, 75% of *Kaletra*-treated patients had fewer than 400 copies/ml of HIV RNA compared with 63% of *Viracept*-treated patients. The percentage of patients with fewer than 50 copies/ml was also significantly higher in the dual protease-inhibitor group. Based on time to virological failure, patients treated with lopinavir/ritonavir had a more durable response than those who received nelfinavir. Both treatment regimens were well tolerated with similar low rates of

discontinuation. While no *Kaletra*-treated patient developed resistant isolates, about one-third of nelfinavir-treated patients with more than 400 copies/ml at some time between week 24 and 48 had isolates with HIV protease mutations. The authors of the report told *Reuters Health* [28 June 2002] that the combination of lopinavir and ritonavir should now be the standard protease inhibitor therapy for the initial treatment of HIV infection.

A related *Perspective*, says that currently the three most commonly prescribed initial antiretroviral regimens are a protease inhibitor (with or without low-dose ritonavir as an enhancer of antiprotease activity) plus two nucleoside reverse transcriptase inhibitors (RTIs); a nonnucleoside RTI plus two nucleoside analogues; and three nucleoside analogues. "Differences in antiviral potency within each of these types of regimens are becoming increasingly discernible" [*Ibid*, 2002-23].

Bupropion for Smoking Cessation in African Americans

African Americans experience smoking-related morbidity and mortality disproportionately. Yet, few clinical trials for smoking cessation in African Americans have been conducted. Extending our knowledge, a recent study compared a sustained-release (SR) form of bupropion with placebo for smoking cessation among African Americans [*JAMA* 2002;288:468-74].

Participants were randomly assigned to receive SR bupropion (n=300) or placebo (n=300) twice

daily for seven weeks. Confirmed abstinence rates at the end of treatment were 36.0% in the bupropion SR group and 19% in the placebo group, an impressive difference. At 26 weeks, however, the quit rates fell to 21.0% in the treated group and 13.7% in the placebo group. The difference in quit rates between treatment and placebo groups at 26 weeks was modest, suggesting that 14 smokers would need to be treated for one smoker to quit successfully.

Prognosis of HIV-Infected Patients Starting HAART

Insufficient data are available from single cohort studies to estimate the prognosis of HIV-infected, treatment-naïve patients who start highly active antiretroviral therapy (HAART). To obtain this information, investigators analyzed data from 13 cohort studies on 12,574 adult patients starting HAART with a combination of at least three drugs. During 24,310 person-years of follow-up, 1094 patients developed AIDS or died and 344 patients died.

Base line CD4 cell count was strongly associated with probability of progression to AIDS or death. Com-

pared with patients starting therapy with less than 50 cells/l, adjusted hazard ratios were 0.74 for 50-99 cells/l, 0.52 for 100-199 cells/l, 0.24 for 200-349 cells/l, and 0.18 for 350 or more CD4 cells/l. Base line viral load was associated with a higher probability of progression only if 100,000 copies or more. Other independent predictors of poorer outcome were advanced age and infection through injection-drug use. The probability of progression to AIDS or death at three years ranged from 3.4% in patients in the lowest risk stratum for each prognostic variable, to 50% in patients in the highest risk stratum [*Lancet* 2002;360:119-29].