



This Week in the Journal

June 27, 2002

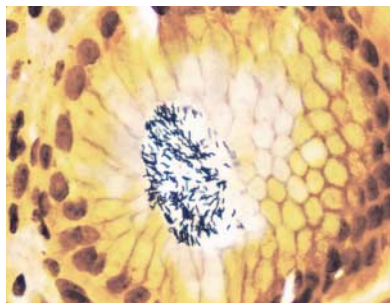
“Current or former use of oral contraceptives among women 35 to 64 years old did not significantly increase the risk of breast cancer.”

Oral Contraceptives and the Risk of Breast Cancer

In a case-control study of the influence of the use of oral contraceptives on the risk of breast cancer, 4575 women who had received a diagnosis of invasive breast cancer and 4682 controls were interviewed about their use of oral contraceptives. There was no evidence that oral-contraceptive use increased the risk of breast cancer.

The findings of this large, detailed investigation, with careful analyses of data, should reassure physicians and women that the use of oral contraceptives does not increase the risk of breast cancer. A noteworthy feature of the study is that the large number of older women who had used oral contraceptives during their reproductive years did not appear to have an increased risk of breast cancer.

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H. pylori in a gastric pit.

Lansoprazole to Prevent Recurrences of Ulcer Complications from Aspirin Use

The use of low-dose aspirin as prophylaxis against cardiac events or stroke and the presence of *Helicobacter pylori* infection are both risk factors for upper gastrointestinal tract bleeding from ulcers. In this study, patients taking low-dose aspirin who had both bleeding from ulcers and *H. pylori* infection had the latter eradicated and were then randomly assigned to receive lansoprazole (62 patients) or placebo (61 patients) and were followed for a median of 12 months while the low-dose aspirin treatment was continued. There was one recurrence of ulcer complications in the lansoprazole group and nine in the placebo group ($P=0.008$).

*These data indicate that after the eradication of *H. pylori* infection in patients who present with ulcer complications, low-dose aspirin therapy can be continued more safely if lansoprazole is added to the therapeutic regimen.*

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PERSPECTIVE

Increasing Choices
for HIV Therapy

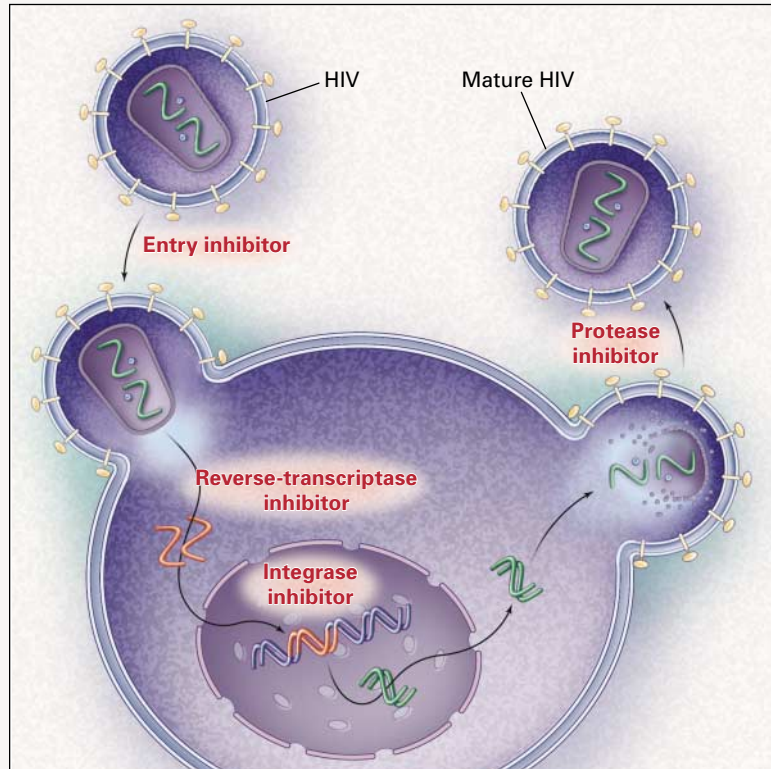
The field of antiretroviral therapy has witnessed remarkable progress during the past 15 years. There are now 16 approved therapeutic agents for infection with the human immunodeficiency virus (HIV), a pathogen that once caused nearly uniformly fatal illness. These agents target two essential enzymes of the virus, the reverse transcriptase and the protease (see Figure). The era of potent antiretroviral therapy, also termed highly active antiretroviral therapy, began in 1996 and has been marked by dramatic declines in morbidity and mortality due to HIV disease in the developed world. These advances have not been without their cost in terms of drug resistance and side effects, particularly metabolic abnormalities such as lipodystrophy. Concern about these negative effects has led to a more conservative approach to the timing of the initiation of therapy and to clinical trials of intermittent therapy in an attempt to decrease the total exposure to drugs over time. Immune-based approaches such as therapeutic vaccination may someday permit viremia to be controlled in the absence of drugs.

Antiretroviral management brings a complex series of choices: when to initiate therapy, what regimen to use, which drugs within each class of drugs to use, when to change therapy, and which alternative drugs to use. In this issue of the *Journal*, Walmsley and colleagues (see pages 2039–2046) report on an important study that illustrates the increasing number of choices facing clinicians and patients. The study compared the efficacy and safety of the most recently approved protease inhibitor, lopinavir (coformulated

with low-dose ritonavir), with the efficacy and safety of nelfinavir in patients who had not previously received antiretroviral therapy and who also received two nucleoside analogues (stavudine and lamivudine). The results demonstrate a consistently superior virologic response over a period of 48 weeks in the lopinavir–ritonavir group, as measured by the proportion of subjects with plasma levels of HIV type 1 (HIV-1) RNA below 400 or 50 copies per milliliter. The durability of the virologic response

and the genotypic drug-resistance pattern of the viral strains from the subjects with virologic failure were also more favorable with lopinavir–ritonavir. There was no difference between the two groups in the CD4 cell response.

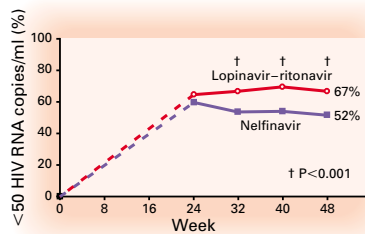
Currently, the three most commonly prescribed initial antiretroviral regimens are a protease inhibitor (with or without low-dose ritonavir as an enhancer) plus two nucleoside analogues; a nonnucleoside reverse-transcriptase inhibitor plus two nucleoside analogues; and three nucle-



The Life Cycle of Human Immunodeficiency Virus Type 1 (HIV-1) and Major Antiviral Targets.

Entry inhibitors (e.g., enfuvirtide, or T-20) and integrase inhibitors are currently under development. Approved reverse-transcriptase inhibitors include the nucleoside analogues (zidovudine, didanosine, zalcitabine, stavudine, lamivudine, and abacavir), a nucleotide analogue (tenofovir disoproxil fumarate), and the nonnucleoside reverse-transcriptase inhibitors (nevirapine, delavirdine, and efavirenz). Approved protease inhibitors include saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, and lopinavir–ritonavir.

Lopinavir–Ritonavir for the Initial Treatment of HIV Infection



In this study of the initial treatment of human immunodeficiency virus (HIV) infection, 653 patients were randomly assigned to treatment with either lopinavir–ritonavir or nelfinavir. All patients also received stavudine and lamivudine. After 48 weeks, there was suppression of HIV RNA to fewer than 50 copies per milliliter in 67 percent of the patients in the lopinavir–ritonavir group, as compared with 52 percent of those in the nelfinavir group ($P < 0.001$).

Lopinavir is a protease inhibitor that has been combined with ritonavir to improve its pharmacokinetic properties. Treatment with this combination was well tolerated and appeared to lead to both effective suppression of HIV replication and less frequent development of resistance mutations. The long-term effects of this drug combination remain uncertain.

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oside analogues. As the study by Walmsley et al. highlights, differences in antiviral potency within each of these types of regimens are becoming increasingly discernible.

How should we incorporate these findings into clinical practice? Should lopinavir–ritonavir now be considered one of the drugs of choice for initial antiretroviral regimens? The answer is not as straightforward as it may appear, for a number of reasons. There is a trend toward prescribing regimens for initial therapy that do not include protease inhibitors, because of concern about metabolic toxic effects. And Walmsley et al. do report a higher incidence of hyperlipidemia in the lopinavir–ritonavir group. Moreover, lopinavir–ritonavir has excellent activity as the core component of alternative regimens in patients in whom initial treatment has failed. Thus, many clinicians may choose to reserve lopinavir for later use. The effects of other approved protease inhibitors — indinavir, saquinavir, and

amprenavir — can all be enhanced with low-dose ritonavir, which creates additional choices for clinicians. In the long-term management of HIV disease, a 48-week study that demonstrates the virologic but not the immunologic superiority of one agent over another represents an important finding, but it may not ultimately translate into the desired clinical outcome many years, and potentially several regimens, later.

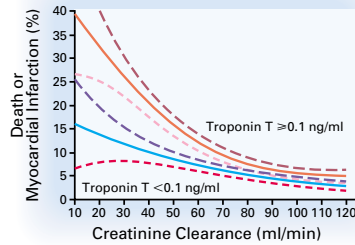
The chief take-home message from the article by Walmsley et al. is that improvements are being made in the potency of antiretroviral drugs, and this bodes well for the future of the field. Antiviral potency is the key to the initial success of drug regimens, as well as to the durability of their success, the restoration of immune function, the prevention of the emergence of resistance, and ultimately the prevention of disease progression. The key is to link potency with the other desirable aspects of a therapeutic regimen: low pill burden, excellent tolerability, absence of major drug

interactions, absence of long-term toxic effects, and absence of cross-resistance to other agents.

Although the article in this issue of the *Journal* highlights the progress that has been made by using the existing classes of antiretroviral drugs, it also reminds us that drug development in the HIV field remains dynamic. Newer antiretroviral agents, such as entry inhibitors and integrase inhibitors, hold great promise. Encouraging clinical results have already been reported for the HIV fusion inhibitor enfuvirtide, or T-20 (see Figure). Future progress in antiretroviral therapy will bring more choices for physicians and patients and will make an already complex field both more challenging and more rewarding.

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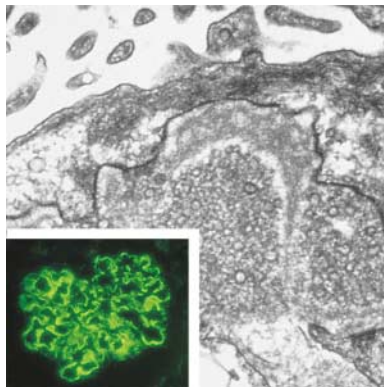


Prognostic Value of Elevated Cardiac Troponin T Levels

Cardiac troponin T levels are commonly used to predict risk in patients in whom acute coronary syndromes are suspected. Because cardiac troponin T is cleared by the kidney, it is uncertain whether it still has prognostic value in patients with renal dysfunction. This study indicates that measurement of cardiac troponin T does predict risk in patients with renal impairment and suspected acute coronary syndromes.

Physicians can now be reassured that the prognostic usefulness of cardiac troponin T levels in patients with acute coronary syndromes is not invalidated by the presence of renal dysfunction.

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Brief Report: Antenatal Membranous Glomerulonephritis Due to Anti-Neutral Endopeptidase Antibodies

The hallmark of membranous glomerulonephritis, a major primary nephropathy, is the presence of immune deposits on the outer aspect of the glomerular basement membrane. The cause of such deposits in humans has eluded detection. The authors of this report studied a neonate whose nephropathy began in utero and who had renal failure and the nephrotic syndrome at birth. Subsequent studies of the infant and his parents documented that alloantibodies had developed in the mother after an earlier miscarriage and that she had a deficiency of neutral endopeptidase. Because she lacked neutral endopeptidase, nephropathy did not develop in the mother, but disease did develop in rabbits that were injected with IgG antibodies from the mother. These antibodies reacted with neutral endopeptidase and were colocalized in subepithelial immune deposits.

Maternal alloimmunization against neutral endopeptidase can lead to neonatal membranous nephropathy.

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Current Concepts: Implantable Devices for Atrial Fibrillation

Overdrive pacing can suppress premature beats and other triggers of atrial fibrillation. Dual-site pacing may help prevent atrial fibrillation. An implantable atrial defibrillator can be programmed and can deliver shocks to terminate atrial tachyarrhythmias and restore sinus rhythm.

The approaches described in this Review Article are beginning to alter the management of atrial fibrillation.

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