HIV Entry Inhibitors Stuck in the Pipeline

BY ROBERT FINN
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SAN FRANCISCO — Efforts to develop entry inhibitors, which constitute the first new class of anti-HIV drugs in years, have hit snags that could delay the entry of these novel agents into the pharmaceutical marketplace.

The debut of entry inhibitors has been eagerly awaited because of preclinical hints that they may be highly effective and have few side effects. But all three entry inhibitors in clinical trials have run into difficulty, and one has now been withdrawn from development, Dr. Steven W. Deeks said at a meeting on HIV management sponsored by the University of California, San Francisco.

GlaxoSmithKline has discontinued its development of Aplaviroc, which appears to have caused at least five cases of liver toxicity. Schering-Plough's vicriviroc did not perform as well as efavirenz in a head-to-head comparison on treatment-naive patients, and is now being developed only for salvage therapy. And a patient taking Pfizer's maraviroc developed liver failure and required a transplant, although there are indications that other drugs the patient was taking might have been to blame.

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Entry inhibitors don't attack the HIV virus directly, explained Dr. Deeks of UCSF. Instead they block a coreceptor on the surface of T cells that the virus requires for entry. Two such coreceptors are known, CCR5 and CXCR4, which are popularly called R5 and X4, respectively. All three investigational drugs target the R5 receptor.

Some people are known to lack the R5 coreceptor because of spontaneous genetic mutations. They seem to harbor no ill effects from this, leading to speculation that agents that block that receptor are unlikely to have serious side effects. No humans are known to lack the X4 coreceptor, on the other hand, and deleting it in mice is lethal. For that reason, there has been a reluctance to develop drugs that bind to the X4 receptor.

R5 viruses are associated with slow disease progression and are common in early HIV disease. X4 viruses are associated with rapid disease progression and emerge in late disease. One worry in using R5 inhibitors is that they may encourage the earlier emergence of X4 viruses. Indeed, this apparently happened in five or six patients in the clinical trials, Dr. Deeks said, and this is likely to be associated with more rapid disease progression.

The difficulties that aplaviroc, vicriviroc, and maraviroc have run into are not related to this, however. Aplaviroc has been associated with five cases of liver toxicity, all of which involved a threefold increase in ALT and a 1.5-fold increase in bilirubin. In all cases, this elevation in enzymes declined when the drug was removed, and in the one case in which the patient was rechallenged with aplaviroc, the liver toxicity recurred. Further development of aplaviroc has been stopped.

There was hope that entry inhibitors might be a good first-line therapy in treatment-naive patients.

But a study comparing Combivir plus efavirenz with Combivir plus vicriviroc in patients who were treatment naive was terminated early because of the clear superiority of efavirenz. Vicriviroc is no longer being developed as a first-line therapy; its use will be only for salvage in patients who have failed earlier regimens.

The case of liver failure in a patient taking maraviroc originally caused concern that studies on this medication would have to be terminated as well. This was despite the fact that the drug has been used in hundreds of treatment-naive and salvage patients with no ill effects. But the patient, a 24-year-old woman, had also been receiving isoniazid and cotrimoxazole for HIV-associated infections. Her ALT levels increased more than fivefold during the 7-week screening period, and her AST increased as well.

On the fifth day of taking maraviroc plus Combivir the patient developed rash and fever, and maraviroc was discontinued. The next day her liver enzymes were significantly elevated (32 times normal). For some reason, despite the known potential for additional liver toxicity, she was given a high dose of acetaminophen (11 g IV) at this time. Her liver enzymes continued to worsen, and on day 16 she received a liver transplant.

Dr. Deeks disclosed relationships with several pharmaceutical companies, including being a recipient of research support from GlaxoSmithKline and working as a consultant for Pfizer. ■

CLINICAL GUIDELINES FOR FAMILY PHYSICIANS

Nonoccupational Postexposure HIV Prophylaxis

BY NEIL S. SKOLNIK, M.D., AND JINN LIU, M.D.

In 1998, the Department of Health and Human Services concluded there was insufficient evidence to recommend for or against nonoccupational postexposure HIV prophylaxis. Since that time, data from studies on nonoccupational postexposure prophylaxis (nPEP) have accumulated, and the guidelines have been updated (MMWR Recomm. Rep. 2005;54:1-20).

Guidelines are most useful when they are available at the point of care. A concise yet complete handheld computer version of this guideline is available for download, compliments of FAMILY PRACTICE NEWS, *at www.redi-reference.com.*

The Evidence

The CDC guidelines are supported by many studies. In one such study, 700 patients were evaluated 12 weeks after nPEP initiation; 7 of the individuals seroconverted. Of those seven, three reported high-risk behavior after starting nPEP, so the seroconversion in these patients may not be entirely due to medication failure.

In studies of mother-to-child HIV transmission, additional benefit appeared to occur when the neonate received prophylaxis in addition to reducing maternal viral load around delivery.

A study of sexual assault survivors in Brazil showed zero seroconversions in the 180 nPEP-treated women compared with four seroconversions in the untreated group of 145 women. Though sample sizes were small and participants not randomly assigned, this study also supports nPEP use.

Recommendations

A 28-day course of a three-drug regimen of highly active antiretroviral therapy (HAART) is recommended for persons with nonoccupational exposure to potentially infected body fluids of a source known to be HIV infected when the exposure represents substantial risk for HIV transmission. Treatment initiation should begin within 72 hours of exposure.

If a source's HIV status is unknown, a decision on whether to begin prophylaxis should be made on a case-by-case basis. nPEP is not recommended for negligible exposure risks or for treatment after more than 72 hours of exposure.

nPEP should be used only for infrequent exposures. Persons engaging in behaviors that result in frequent, repeated exposure should not take nPEP and instead should be provided with intensive risk-reduction interventions.

Although studies demonstrate that nPEP is less likely to prevent HIV transmission when initiated more than 72 hours after exposure, it cannot be concluded that nPEP is completely ineffective when initiated after 72 hours from exposure; therefore, clinicians might consider prescribing nPEP after exposures that present a serious risk for transmission.

Treatment

Based on experience with individual agents in the treatment of HIV-infected persons, preferred regimens include efavirenz plus lamivudine or emtricitabine with zidovudine or tenofovir (a nonnucleoside-based regimen).

Another treatment option is lopinavir and ritonavir plus zidovudine, with either lamivudine or emtricitabine (a protease inhibitor–based regimen). The recommendations for a three-drug HAART regimen are based on the assumption that maximal suppression of viral replication will provide the best chance for preventing infection.

Other Considerations

Adherence to antiretroviral medications is challenging. Common side effects include nausea and fatigue, and each dose reminds the patient of his or her risk for acquiring HIV infection.

Patients seeking care after HIV exposure should be tested for HIV antibodies at baseline, 4-6 weeks, 3 months, and 6 months after treatment initiation to determine HIV seroconversion. Testing for sexually transmitted diseases, hepatitis B and C, and pregnancy should also be offered. In patients undergoing nPEP, liver function, renal function, and hematologic parameters should be monitored.

If possible, the source should be interviewed to determine the history of antiretroviral use and most recent viral load. This information may be useful when choosing nPEP medications. The risk for transmission might be especially great if the source has been infected recently because his viral load in the blood and semen is particularly high.

Special Populations

Clinicians should consult CDC guidelines before nPEP treatment in pregnant women. Efavirenz should not be used during pregnancy or among women of childbearing age at risk for becoming pregnant because of potential teratogenicity. The combination of d4T with ddI has also been associated with lactic acidosis causing fetal mortality.

For appropriate nPEP regimens in children, refer to the American Academy of Pediatrics or CDC guidelines.

The Bottom Line

A 28-day course of HAART is recommended for persons seeking care within 72 hours from nonoccupational exposure to potentially infectious body fluids of a known HIV-infected source when the exposure represents a substantial risk for transmission.

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