



MK-0518 and GS-9137: *Two Promising Integrase Inhibitors in the Pipeline*

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Possibly the most exciting news to come out of the 13th Conference on Retroviruses and Opportunistic Infections, held in Denver last February, concerned clinical trials of two experimental drugs in a new class: integrase inhibitors. If successful in further trials, integrase inhibitors could revitalize the treatment regimens of people living with multidrug-resistant HIV.

Integrase and Integrase Inhibitors

Highly active antiretroviral therapy (HAART) currently incorporates four classes of anti-HIV drugs: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and entry/fusion inhibitors. Integrase inhibitors may represent a fifth class—welcome news for people with drug-resistant HIV.

“Ten years after the introduction of combination therapy for HIV, we are seeing an increase in the number of patients whose virus has developed resistance to many of today’s drugs,” notes Edwin DeJesus, MD, of the Orlando Immunology Center in Florida. “New and better options are desperately needed, particularly among treatment-experienced patients who must often take complex regimens.”

Three of the existing antiretroviral classes target reverse transcriptase and protease—two enzymes that HIV needs for replication. Integrase is a third enzyme which integrates viral genetic material into the host cell’s DNA, permitting the infected cell to produce new copies of the virus (see sidebar on page 14).

HIV researchers have been studying the role of integrase in viral replication for more than 15 years, with the goal of creating drugs to target the enzyme. To this end, scientists had to design an assay, or screening system, to

identify chemical compounds that inhibit the activity of the integrase enzyme. A complicating factor in the screening process is that integration is a multistep process—and a potential integrase inhibitor could be active during any stage. Early laboratory tests gave many false-positive results for compounds that were later shown to have no antiretroviral activity in human cells.

Early preclinical studies and clinical trials were also disappointing. In 1995, researchers at Aronex Pharmaceuticals (now owned by Antigenics Incorporated) thought they had discovered a promising integrase-targeting agent in a compound called AR-177. But further study showed that this experimental drug did not actually interfere with DNA integration. Clinical trials of the compound were ultimately discontinued due to poor results. Other candidates followed, but also were unsuccessful; for example, Shionogi/GlaxoSmithKline’s S-1360 was terminated because the drug showed poor bioavailability, and Merck’s L-870810 was discontinued due to toxicity with long-term dosing in animal studies.

However, two other integrase inhibitors in the antiretroviral pipeline are showing great promise, and they act in ways that set them apart from their predecessors. Integration proceeds in three stages: the integrase enzyme first binds to the host cell’s DNA, then processes a specific region on the strand of viral DNA (created through reverse transcription), and finally transfers this strand into the host cell. Early attempts to design an integrase inhibitor (such

Three Important Enzymes

HIV replication is a multistep process that relies on three enzymes:

Reverse transcriptase “transcribes” viral genetic material from RNA to DNA early in the replication process.

Integrase binds to the newly created DNA and integrates it into the host cell’s own genetic material, enabling the host cell to start producing viral proteins—the raw material for new copies of the virus.

Protease cleaves (cuts up) these large proteins into component parts that can then be assembled into new viral particles.

as AR-177) focused on the initial binding step, whereas the two new experimental drugs from Merck and Gilead Sciences target the third step: strand transfer.

Two Strand-Transfer Inhibitors: MK-0518 and GS-9137

Screening potential integrase-inhibiting compounds for activity during the strand-transfer stage paid off: in a proof-of-concept study published in 2000, Merck researcher Daria Hazuda, PhD, reported on diketo acids, chemical compounds that successfully inhibited the strand-transfer step of integration in rhesus macaques (monkeys commonly used to model disease progression and test treatments in preclinical trials). In subsequent studies, one such compound, named L-870812, was potent against HIV strains with resistance to the three major classes of antiretroviral drugs (NRTIs, NNRTIs, and PIs). Furthermore, when researchers cultivated strains resistant to the experimental integrase inhibitor, the cultured virus had only limited ability to replicate.

Thus, Hazuda and colleagues had discovered an integrase-targeting agent that both disrupted viral replication and was active against drug-resistant HIV *in vitro* and in animals. The researchers concluded that integrase inhibitors represent “a new class of agents to treat HIV-1 infection in therapy-naïve patients and patients harboring viruses resistant to current antiviral agents.”

MK-0518

Based on Hazuda and colleagues’ research and subsequent studies, Merck scientists developed MK-0518, the first integrase inhibitor to reach Phase II clinical trials. In a study presented at the 2005 European AIDS Clinical Society meeting in Dublin, volunteers taking the MK-0518 pill as

monotherapy for ten days achieved a 98% reduction in HIV RNA, and at least half of the trial participants saw their viral load drop to 400 copies/mL or less.

The drug was also well tolerated: the most common side effects reported by study volunteers were headache, fatigue, and dizziness, and these were comparable in the groups receiving MK-0518 and placebo. There were no serious adverse events, and no participants discontinued the study because of side effects.

In light of these encouraging results, an international team of researchers, led by Beatriz Grinsztejn, MD, of the Evandro Chagas Clinical Research Institute in Rio de Janeiro, embarked upon a dose-ranging trial of MK-0518 plus optimized background therapy (OBT) vs placebo plus OBT in treatment-experienced individuals. Results from the multicenter, randomized, double-blind Phase II study were presented at the February Retrovirus conference (*abstract 159LB*).

Volunteers entered the trial with viral loads of at least 5000 copies/mL, had been on antiretroviral therapy for at least three months, and had HIV strains resistant to NRTIs, NNRTIs, and PIs. Participants also had CD4 counts greater than 50 cells/mm³. Subjects were divided into a placebo group and three dose cohorts—receiving 200 mg, 400 mg, or 600 mg of MK-0518 orally twice daily—and all groups (including placebo) received OBT regimens tailored to each participant’s antiretroviral history and drug-resistance profile.

Because atazanavir (Reyataz), a drug included in some participants’ background regimens, is known to elevate levels of MK-0518 in the blood, data were also gathered on two subgroups—participants who received atazanavir and those who did not—in each dose cohort.

After 16 weeks of therapy, dramatic declines were observed in the viral loads of participants taking the experimental integrase inhibitor: HIV RNA decreased to less than 400 copies/mL in 84% of the 200-mg cohort, 73% of the 400-mg cohort, and 67% of the 600-mg cohort, compared with only 24% of individuals receiving placebo. (These percentages suggest that lower doses were more effective, but the investigators found that the difference was not statistically significant.)

In addition, *all* participants receiving 200 mg or 600 mg of MK-0518 plus atazanavir saw their viral loads drop

BIOAVAILABILITY
the degree to which a drug or other substance is absorbed and circulated in the body.

to less than 400 copies/mL (vs 33% in the placebo group), compared with 86% and 91%, respectively, of their dose-cohort counterparts who did not receive atazanavir (vs only 23% of those on placebo and OBT without atazanavir). MK-0518 was also shown to raise CD4 cell counts.

Drug-related adverse events were mild, the most common being gastrointestinal symptoms, fatigue, headache, flushing, itching, and injection site reactions related to OBT containing T-20 (enfuvirtide, Fuzeon). There were no dose-related adverse events, and the two discontinuations (one due to lack of response to treatment, and one unrelated death) also were not dose-related. The researchers concluded that MK-0518 is well tolerated and significantly suppresses viral replication in treatment-experienced HIV positive individuals.

GS-9137

Another integrase inhibitor in the pipeline is Gilead's GS-9137, also called JTK-303. Gilead purchased the rights to develop the drug from Japan Tobacco in March 2005 and initiated clinical trials the following June (Japan Tobacco retains the rights to develop the drug in Japan). Two Phase I/II trials of GS-9137 were described at the Retrovirus conference.

Results of a study by Isao Kawaguchi of Japan Tobacco and colleagues (*abstract 580*) on the experimental drug's safety and pharmacokinetics in HIV negative individuals suggest that GS-9137 is safe, orally bioavailable (especially when administered with food), and well tolerated at once-daily doses of 100 mg, 200 mg, 400 mg, or 800 mg. Taking the pill with food yielded a three-fold increase in drug concentration in the blood. No severe adverse events were reported.

Even more encouraging is another GS-9137 study (*abstract 160LB*), described at the conference by DeJesus, which evaluated the safety, pharmacokinetics, pharmacodynamics, and antiretroviral activity of the drug in HIV positive volunteers. This prospective, randomized, double-blind, placebo-controlled study involved 40 treatment-naïve and treatment-experienced participants, none of whom were taking antiretroviral medications at the start of the trial. Participants entered the study with viral loads of 10,000 to 300,000 copies/mL and CD4 cell counts of no greater than 200/mm³.

Ten study participants were given placebo and 30 participants (15 treatment-experienced and 15 treatment-naïve) received the integrase inhibitor for ten days as monotherapy in one of five dose cohorts: 200 mg, 400 mg, or 800 mg twice daily; 800 mg once daily; or 50 mg boosted with 100 mg of ritonavir (Norvir) once daily.

PHARMACOKINETICS

how drugs are processed and used in the body, including absorption, metabolism, distribution to tissues, and elimination.

PHARMACODYNAMICS

the biochemical and physiological effects of drugs in the body.

All dose cohorts showed excellent viral suppression compared with the placebo group. Participants in the twice-daily 400-mg and 800-mg cohorts and in the once-daily boosted 50-mg cohort responded best, with a roughly 2-log (approximately 99%) reduction in viral load. Among these participants, 50% experienced even greater decreases in viral load.

Also exciting is the potential for once-daily dosing. Concentrations of GS-9137 rose dramatically when boosted with ritonavir, with a 20-fold increase in oral bioavailability and a half-life of approximately nine hours—raising the possibility of a once-daily pill and simplified combination regimens.

Next Steps

Given these promising results, both integrase inhibitors are now undergoing more extensive clinical trials. Longer studies with more participants, as well as post-study follow-up, will elucidate the long-term tolerability of the two investigational agents and the durability of their antiretroviral effects.

The studies described at the 2006 Retrovirus conference did not pit the experimental integrase inhibitors against PI-resistant virus. Gilead is currently conducting a clinical trial to evaluate the issue; this multicenter, randomized, double-blind study is assessing the effects of GS-9137 boosted with ritonavir vs a ritonavir-boosted PI as part of combination therapy in 200 individuals with PI-resistant HIV.

Studies of Merck's integrase inhibitor are also expanding. Two international, multicenter, randomized, double-

LOG

a measure that refers to quantities as a factor of ten. A log change is an exponential or ten-fold increase or decrease. Changes in viral load are often expressed in logs.

blind, placebo-controlled Phase III trials are underway to assess the safety and efficacy of MK-0518 plus OBT vs OBT alone in individuals with drug-resistant HIV. The U.S. trial (Study 2005_097) is expected to enroll more than 300 participants, with a treatment duration of 48 weeks. (See “Open Clinical Trials,” page 49, for details.)

In a February 9, 2006 article in the *San Francisco Chronicle*, Robin Isaacs, MD, Merck’s executive director of infectious disease and HIV vaccine clinical research, expressed hope that Merck would apply for Food and Drug Administration approval in the second half of 2007.

Hope for the Future

After the success of the Phase I/II trial of GS-9137, DeJesus is eyeing other agents in the antiretroviral pipeline—such as entry inhibitors—as potential candidates for combination therapy. If integrase inhibitors and new entry inhibitors are administered with the fusion inhibitor T-20, the combination “could potentially offer highly experienced patients the opportunity to receive three drugs for which they may have full sensitivity.”

Equally optimistic is Paul Sax, MD, director of the HIV program at Boston’s Brigham and Women’s Hospital and assistant professor at Harvard Medical School. In an interview at the Retrovirus conference, Sax called study participants’ responses to the Merck integrase inhibitor “dynamite,” and observed that data on multiple experimental agents presented at the meeting show promise of helping people who are currently on salvage therapy: “You can imagine someone getting the Merck or the Gilead integrase inhibitor plus TMC114 [darunavir], plus Panacos’ maturation inhibitor [bevrimat, PA-457], plus maraviroc, the CCR5 antagonist—all these different options for people who have drug resistance.”

Reilly O’Neal is the editor of *BETA*.

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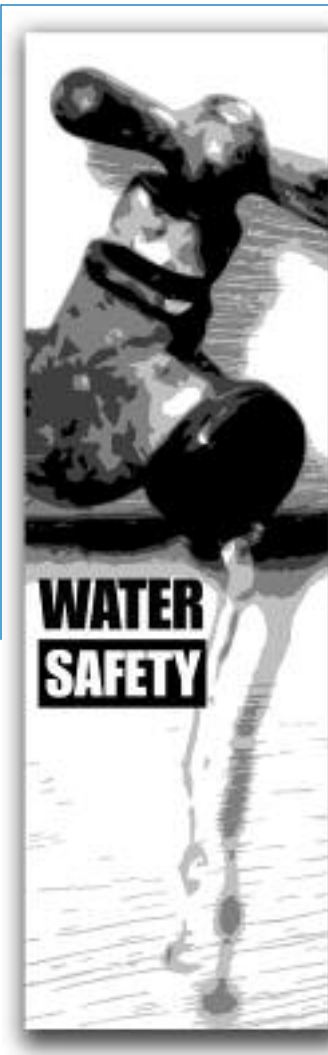
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HIV positive people are advised to drink purified water to help avoid *Cryptosporidium parvum* and other microscopic parasites.

Boiling is perhaps the best way to ensure water safety. On the stove or in a microwave-safe container, heat water at a rolling boil for one minute. Allow water to cool, then store it in the refrigerator in a clean bottle or pitcher with a lid.

Faucet-mounted water filters are convenient for home use. Be sure to check the box for the words “reverse osmosis” or “absolute one micron.” For a list of filters that remove *Cryptosporidium*, contact NSF International (info@nsf.org; 877-867-3435).

Bottled water brands may not identify their purification method on the label. When in doubt, call the manufacturers (the telephone number is often listed on the packaging) and ask whether their treatment system removes *Cryptosporidium*.

Remember, water safety includes using boiled or otherwise treated water for cooking and making ice. **DRINK UP!**