



Two New Pharmacoenhancers Give HAART a Boost

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Clinicians typically try to avoid drug-drug interactions because they can alter medication levels in the body in ways that can either decrease effectiveness or increase toxicity and side effects. But one type of interaction—known as “boosting”—can enhance effectiveness and lower drug doses.

Abbott Laboratories’ ritonavir (Norvir) was the first, and currently is the only, agent used to boost antiretroviral drugs. But two investigational “pharmacoenhancers” discussed at the 16th Conference on Retroviruses and Opportunistic Infections (CROI) this past February—GS-9350 from Gilead Sciences and SPI-452 from Sequoia Pharmaceuticals—may offer additional boosting options and new opportunities for developing fixed-dose combination pills.

How Does Boosting Work?

Many types of drugs are processed by a family of related enzymes (isoenzymes) in the liver known as the cytochrome P450, or CYP, system.

A given drug may *inhibit* the activity of one or more of these isoenzymes, which causes other medications processed by the same enzymes to be cleared more slowly from the body; this allows these drugs to build up to higher concentrations that can result in worse side effects. Conversely, an agent may *induce* the activity of isoenzymes, thereby speeding up processing and clearance of other drugs; this can lead to lower drug concentrations that may be less effective and may enable the emergence of drug-resistant virus.

The protease inhibitor (PI) ritonavir—one of the most potent CYP inhibitors—binds strongly to the CYP3A isoenzyme and renders it unavailable for processing other drugs. CYP3A is responsible for metabolizing a wide range of drug classes, including certain other HIV PIs, non-nucleoside reverse transcriptase inhibitors, and integrase inhibitors. Ritonavir therefore interacts with numerous HIV medications, and it may also affect concentrations of non-HIV drugs, such as methadone, many psychiatric medications, and some of the cholesterol-lowering statins.

Ritonavir Boosting

In the late 1990s, researchers discovered that adding a small amount of ritonavir increased the bioavailability of other first-generation PIs such as saquinavir (Invirase) and indinavir (Crixivan). This greatly lowered pill burdens and allowed dosing frequency to be reduced from once every eight hours to once or twice daily.

In 2000, the Food and Drug Administration (FDA) approved Abbott’s Kaletra, which combines the company’s PI lopinavir with a boosting dose of ritonavir in a single pill. Individuals using PIs produced by other manufacturers must take ritonavir separately, thereby increasing costs.

Activists protested vociferously in 2003 when Abbott raised the price of the boosting dose of ritonavir—which is no longer widely used at full doses due to toxicities and undesired drug interactions—by about 400%. Since that time, researchers and patient advocates have sought alternative boosters in an effort to avoid the metabolic and gastrointestinal side effects associated with even small amounts of ritonavir, and pharmaceutical companies have endeavored to develop such agents to combine with other drugs in their own formularies.

“Boosting PIs was a breakthrough that depends on one molecule, ritonavir,” CROI chair John Mellors of the University of Pittsburgh stated at a conference press briefing.

“This has been a bottleneck, and there has been a hue and cry over having only one boosting agent, and concern at the regulatory level and among clinicians.”

GS-9350

At a CROI session on antiretroviral pharmacology and complications, Brian Kearney, Gilead’s Senior Director of Clinical Research, presented early data on GS-9350, a pharmacoenhancer that works by the same mechanism as ritonavir, but is not itself active against HIV.

Gilead does not produce a PI of its own that requires boosting, but has sought an agent to enhance the bioavailability of its investigational integrase inhibitor elvitegravir (formerly GS-9137), which—unlike the approved integrase inhibitor raltegravir (Isentress)—requires boosting to reach an optimal therapeutic concentration; early clinical trials of elvitegravir have used ritonavir as a booster.

In preclinical laboratory studies, GS-9350 inhibited CYP3A activity and slowed drug clearance in cultured human liver cells; furthermore, GS-9350 appeared to be a more specific inhibitor of CYP3A than ritonavir, with less effect on other isoenzymes.

GS-9350 demonstrated no activity against HIV even at high concentrations. At doses that could realistically be used in patients, it did not promote lipid accumulation in adipocytes (fat cells) and only minimally interfered with glucose uptake (absorption of sugar) by the body’s cells.

Following these promising laboratory findings, GS-9350 moved into Phase I clinical trials. In study GS-216-0101, a total of 36 healthy HIV negative volunteers were randomly assigned to receive once-daily GS-9350 (50 mg, 100 mg, or 200 mg), ritonavir (100 mg), or placebo, either as a single dose or as multiple ascending doses administered over a 14-day period.

GS-9350 inhibited clearance of midazolam—a known CYP3A substrate used as a “probe” to measure boosting ability—by 92% at 100 mg and by 95% at 200 mg, similar to the 95% inhibition observed with ritonavir.

Single and multiple doses of GS-9350 were generally well tolerated, with no drug-related serious (grade 3 or 4) laboratory abnormalities or grade 4 clinical adverse events (the sole grade 3 clinical event was “discoordination” in a woman who reported that she had difficulty juggling while taking the drug). Finally, GS-9350 was said to have little taste, in contrast with the notoriously bitter ritonavir.

Quad Combination Pill

Following this proof-of-concept trial, Gilead scientists devised fixed-dose coformulation pills containing 100 mg or 150 mg GS-9350 plus 150 mg elvitegravir, 300 mg tenofovir (Viread), and 200 mg emtricitabine (Emtriva). This “quad”

pill offers a complete once-daily antiretroviral regimen in a single pill smaller than Atripla, the tenofovir/emtricitabine/efavirenz combination pill.

In the open-label Phase I study GS-236-0101, a total of 44 HIV negative participants received versions of the quad pill. Both the 100 mg and 150 mg GS-9350 coformulations boosted plasma levels of elvitegravir. The higher dose produced elvitegravir concentrations previously determined to be therapeutic against HIV in studies with ritonavir, and maintained an adequate level between doses.

Again, the treatment was generally well tolerated, with no drug-related grade 3 or 4 clinical adverse events and no grade 4 laboratory abnormalities (the sole grade 3 abnormality was a transient aspartate aminotransferase [AST] elevation). No changes in blood lipid levels were seen in this short study.

SPI-452

At the same conference session, Robert Guttendorf from Sequoia Pharmaceuticals presented data on the company’s investigational pharmacoenhancer SPI-452. Like Gilead, Sequoia has sought to develop a boosting agent that works like ritonavir to slow drug processing, but with better tolerability and no anti-HIV activity. The company is also testing SPI-452 as a potential booster for Schering-Plough’s experimental hepatitis C virus PI boceprevir, currently in Phase III trials.

In preclinical studies, SPI-452 inhibited metabolism of approved HIV PIs, as well as boceprevir, in human liver cell cultures. In rats and dogs, SPI-452 potently inhibited CYP3A and boosted concentrations of saquinavir, lopinavir, and atazanavir (Reyataz).

In the first human clinical trial, study 0452-001, a total of 58 healthy HIV negative volunteers first received single ascending doses of SPI-452 (25 mg, 50 mg, 100 mg, 200 mg, 400 mg, and 600 mg). Participants were then assigned to receive either 50 mg or 200 mg SPI-452 plus 1000 mg saquinavir, or saquinavir alone, or placebo alone.

Guttendorf characterized SPI-452 pharmacokinetics as “fairly well behaved,” and the booster increased concentrations of saquinavir in a dose-dependent manner, indicating that it was “hitting its molecular target.” SPI-452 was generally well tolerated at single doses up to 600 mg, both alone and in combination with saquinavir. Adverse events were typically mild and no severe events were observed. The most frequently reported adverse events were headaches and sore throat.

In study 0452-002, a Phase I proof-of-concept trial, 67 HIV negative volunteers first received single doses of 600 mg darunavir (Prezista) or 300 mg atazanavir or placebo, in order to establish PI plasma concentrations. After a 7-day

washout period (during which no drug was taken), participants were randomly assigned to receive 25 mg, 50 mg, or 200 mg SPI-452 or placebo once daily for 15 days, followed by a day on the PIs plus placebo.

Coadministration of SPI-452 increased minimum plasma concentrations of darunavir by up to 37-fold and atazanavir by up to 13-fold, and the boosting effect was durable through day 16 (the day after the last dose).

Again, SPI-452 was generally well tolerated at doses of up to 200 mg for 15 days, with no severe adverse events and no significant changes in laboratory parameters, liver function tests, blood lipid levels, or electrocardiograms (ECGs). In this study, the most commonly reported adverse events were headaches and gastrointestinal symptoms (nausea, vomiting, diarrhea). Guttendorf noted that participants were instructed to stop consuming caffeine during the study, which can cause headaches.

Future Directions

In an April press release, Gilead announced that it has started a head-to-head Phase II trial of the 150-mg GS-9350 version of the quad pill in comparison with Atripla. The 48-week study aims to enroll 75 treatment-naïve patients at 50 U.S. sites. After the 48-week blinded study is completed, participants will have the option to continue in an open-label rollover extension phase.

“The single-dose regimen of Atripla has become the standard of care for many patients, particularly those new to therapy,” said Norbert Bischofberger, Gilead’s Chief Scientific Officer. “If proven safe and effective, this new single-tablet regimen has the potential to provide an important alternative for them.”

The quad pill may offer an option for individuals who cannot take Atripla, including people who experience intolerable neuropsychiatric side effects from efavirenz, as well as pregnant women, who should avoid taking efavirenz

due to its association with increased risk of birth defects, especially during the first trimester. (The quad pill’s safety and efficacy during pregnancy have not been established, however.)

Gilead is also studying GS-9350 as a stand-alone boosting agent, including a Phase II trial of GS-9350 as a booster for atazanavir, building on the path-breaking intercompany collaboration with Bristol-Myers Squibb that produced Atripla.

Likewise, Guttendorf noted that Sequoia plans to move forward with further clinical trials of SPI-452 as a stand-alone boosting agent and as a component of fixed-dose co-formulations. The company currently has no FDA-approved antiretroviral drugs, but has an HIV PI (SPI-256) in Phase I development, suggesting that a combination pill might be in the works.

Beyond HIV and hepatitis C, Guttendorf said that SPI-452 and other pharmacoenhancers in earlier stages of development might have potential as boosters of drugs for nonviral diseases that are metabolized by the CYP system.

“The treatment activist community is delighted that there are protease inhibitor boosters other than [ritonavir] on the horizon,” said Lynda Dee of the Fair Pricing Coalition (FPC). “The FPC anxiously awaits the time when [ritonavir] is but one of the boosting alternatives available to HIV patients, the time when Abbott will no longer be able to hold the HIV community hostage because it owns the one and only PI booster.”

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Selected Sources

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