

Aids Conference

The latest scoop

Reports from AIDS 2010 and ICAAC on new drugs in the pipeline

by Chrystal Palaty

Hope continues to spring eternal for new HIV therapies. We reported on drugs in the pipeline earlier this year in Issue 64 of *Living Positive*. Updates at the XVIII International AIDS Conference (AIDS 2010) in Vienna in July 2010, and at the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in Boston in September 2010 brought further promise. The treatments in the pipeline include new drugs as well as strategies for combining these new drugs with existing drugs. While there are many treatments at various phases of development, the new drugs discussed below are furthest along in development.

New integrase inhibitors

Integrase inhibitors are drugs that block the activity of the integrase enzyme, preventing HIV from integrating into the DNA of an infected cell. Currently, raltegravir (Isentress) is the only integrase inhibitor approved, and while it's generally well tolerated, HIV can become resistant to raltegravir after people have been on therapy for a while. For this reason, drug companies are working to come up with alternative integrase inhibitors.

Elvitegravir is an integrase inhibitor in development by Gilead Sciences. It's currently in phase III clinical trials. Although elvitegravir requires boosting, it's administered only once a day, and because it's eliminated through the feces instead of the urine, it may be a good choice for people with kidney issues. The downside of

this drug is that people who are resistant to raltegravir are also likely to be resistant to elvitegravir. This new drug is one component of Gilead's new quad pill.

GSK-1349572 is a second-generation integrase inhibitor by ViiV Healthcare, now in phase II trials. Unlike raltegravir and elvitegravir, this integrase inhibitor is administered once a day without boosting. Results of a phase IIb dose-ranging study showed no severe adverse events, which is very promising. While this drug can reduce viral loads in people with raltegravir-resistant HIV, the specific type of raltegravir resistance mutation influences how effective the drug is. Phase III studies in integrase inhibitor-naïve people are starting in late 2010.

A second integrase inhibitor being developed by ViiV Healthcare is S/GSK-1265744. This drug is also in phase II trials and is effective against raltegravir-resistant HIV, but has less potency than GSK-1349572.

LEDGINs, or 2-(quinolin-3-yl) acetic acids, are second-generation integrase inhibitors with a different mechanism of action than the others. Instead of inhibiting integrase enzymes, these drugs inhibit a host protein that's responsible for bringing the virus and infected cell DNA together. LEDGINs are effective against raltegravir- and elvitegravir-resistant HIV, and early work shows that they have low toxicity. These are still in preclinical development, and much further back in the pipeline, but are an exciting alternative to raltegravir.

A new booster with fewer side effects

Boosters are drugs that increase the activity of other drugs by inhibiting the metabolic enzymes that break them down. Currently, ritonavir (Norvir) is used to boost levels of protease inhibitors, but causes long-term side effects such as elevated lipid levels and gastrointestinal issues.

Cobicistat (GS-9350) is being developed by Gilead Sciences as a potential alternative to ritonavir. This once-daily formulation uses the same mechanism of action as ritonavir, and phase II trials comparing cobicistat and ritonavir have demonstrated that while both drugs have similar activity in decreasing viral loads, cobicistat caused fewer side effects.

However, people taking cobicistat showed an increase in serum creatinine, which is sometimes an indicator of kidney toxicity. Researchers conducted a study on healthy volunteers, and the results showed that cobicistat inhibits the secretion of creatinine, but it isn't toxic to the kidneys. Phase III trials are underway, comparing cobicistat to ritonavir with various combinations of other drugs.

The quad combination pill

Gilead Sciences is developing a new quad pill as a potential replacement for efavirenz/emtricitabine/tenofovir (Atripla) for people who have never taken antiretrovirals. This pill consists of two antiretrovirals, emtricitabine (Emtriva) and tenofovir (Viread), in addition to elvitegravir and cobicistat.

Recent phase II clinical trials compared the new quad with Atripla over a 48-week period and demonstrated that the new drug had similar efficacy, but with some differences in side effects. People taking the new quad had slightly higher CD4 counts and experienced fewer dreams with less dizziness, fatigue, and difficulty concentrating.

While lipid levels increased for people on either pill, those on the new quad pill had a slightly different lipid profile—different proportions of the different lipid components—than people on Atripla. Serum creatinine was higher in people taking the quad pill due to the cobicistat. Phase III trials with the quad are underway. A number of other combination pills are also in development.

New entry inhibitors

Entry inhibitors, also called CCR5 antagonists, prevent HIV from entering uninfected cells by blocking the main HIV-1 entry co-receptor, CCR5. Currently, maraviroc (Celsentri) is the only drug of this type available, but before the drug is prescribed, an expensive assay needs to

be done in order to confirm the drug will be effective.

TBR-652 is a new CCR5 antagonist in development, which blocks both CCR5 as well as the CCR2 receptor. This drug is taken orally, with once-daily dosing. In a short-term study, it was well tolerated and had excellent results. TBR-652 may potentially have anti-inflammatory activity because it can inhibit CCR2, which is associated with a number of inflammation-related diseases, however there's no actual proof of this yet. At the AIDS conference, some attendees raised concerns about this anti-inflammatory characteristic, as a reduced inflammatory function may lead to a risk of infection.

Other CCR5 antagonists are also in development, including PRO 140 from Progenics Pharmaceuticals, ibalizumab (TMB-355) from Genetech, and HGS004 from Quest Clinical Research. Vicriviroc (previously named SCH 417690; SCH-D) was another CCR5 antagonist that was in development, however it's no longer investigated.

Non-nucleoside reverse transcriptase inhibitors

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) structurally alter the reverse transcriptase enzyme, preventing synthesis of the HIV DNA. Rilpivirine (TMC278) is a second-generation non-nucleoside reverse transcriptase inhibitor for treatment-naïve people; it's currently in phase III trials. Overall, rilpivirine has similar efficacy to efavirenz (Sustiva), but with less incidence of side effects. ☺

For more information

Additional information about these and many other developments can be found at:

- ▷ "Antiretroviral Medications in the Pipeline," www.thebody.com/content/treat/art58303.html
- ▷ "Other Antiretroviral Drugs in Development," www.thebody.com/content/art6079.html
- ▷ CATIE's Treatment Update, www.catie.ca/tu.nsf

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