Two antiretroviral medicines recently came on the scene for people starting HIV treatment for the first time: Rilpivirine (brand name Edurant) won marketing approval in May, and the following August saw approval of Complera, a single-pill once-daily regimen that joins rilpivirine with two other drugs.

This article explains the science behind rilpivirine and Complera and how these drugs measure up to the commonly prescribed efavirenz (Sustiva) and Atripla.

Old Class, New Agent
Rilpivirine, formerly known as TMC278, is the first new antiretroviral drug to be approved by the United States Food and Drug Administration (FDA) in three years. It joins four other drugs in the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, the oldest of which has been around since 1996.

NNRTIs work by interfering with an early stage in viral replication. Once inside a human CD4 T-cell, HIV uses an enzyme called reverse transcriptase to convert its own genetic material, ribonucleic acid (RNA), into deoxyribonucleic acid (DNA), the same form of genetic material contained in the human cell. NNRTIs attach to reverse transcriptase, blocking this crucial early step and preventing HIV from replicating.

The popularly prescribed NNRTI efavirenz (Sustiva) was approved in 1998 and has proven highly effective at reducing viral load—so much so that the widely used Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, published by the U.S. Department of Health and Human Services (DHHS), currently lists efavirenz plus tenofovir/emtricitabine as the “preferred” NNRTI-based regimen for people starting antiretroviral therapy (ART) for the first time.

In fact, the DHHS guidelines have listed efavirenz as a component of preferred starter regimens since 1998—a reflection of the drug’s potency and long-lasting effects. Yet efavirenz has downsides, most famously its association with central nervous system side effects like dizziness and abnormal dreams or nightmares. Serious psychological side effects have also been reported in a minority of people; the efavirenz product package insert notes that clinical trials have found a higher frequency of severe depression (2.4% vs. 0.9%) among efavirenz takers compared with participants not taking efavirenz. (See “Making Sense of Side Effects,” page 19, for more about adverse events related to efavirenz.)

Like any drug, efavirenz has its trade-offs and is not right for everyone. For this reason, approval of a potent and tolerable new NNRTI is particularly welcome. So, how does rilpivirine stack up against its older classmate?

Evidence from Clinical Trials
Two advanced clinical trials assessing the safety, tolerability, and efficacy (how well the drug works in a trial setting) of rilpivirine were reported in the July 16, 2011, issue of The Lancet. The Phase III ECHO and THRIVE trials compared rilpivirine with efavirenz, both taken once daily with a background regimen, in a total of 1,368 treatment-naive HIV positive participants.

ECHO and THRIVE
In the ECHO study, 346 participants were randomly assigned to take 25 mg rilpivirine (the ultimately approved daily dose) and 344 were randomized to receive the standard 600-mg dose of efavirenz. By week 48, 83% of all participants—those taking rilpivirine and those on efavirenz—
had experienced “virological response,” meaning they saw their viral load drop below 50 copies/mL.

This finding lead the researchers to conclude that rilpivirine’s efficacy is non-inferior to efavirenz. (Non-inferiority studies are designed specifically to show that one agent performs as well as another.)

Virological “failure,” defined as either the failure to reach an undetectable viral load or viral rebound, occurred in more people taking rilpivirine than efavirenz (13% vs. 6%, respectively), however.

Among participants who started the study with a viral load below 100,000 copies/mL, 90% of those on rilpivirine and 83% of those on efavirenz saw their viral load drop below 50 copies/mL by week 48. However, people who started with higher viral loads fared better on efavirenz. Among those with a baseline viral load between 100,000 and 500,000 copies/mL, 79% of participants on rilpivirine and 83% on efavirenz achieved undetectable viral load. The difference was even more marked among those with greater than 500,000 copies/mL at treatment initiation: 62% compared with 81% for the rilpivirine and efavirenz arms, respectively.

Unsurprisingly, adherence was linked with viral suppression in both study arms. Among participants who reported better than 95% adherence (meaning they took their pills on more than 95% of all the days they were in the trial), rates of virological response were comparable between study arms (86% with rilpivirine and 87% with efavirenz). Among participants with self-reported lower adherence (at or under 95%), fewer rilpivirine takers than those on efavirenz (68% vs. 73%) achieved viral load below 50 copies/mL.

“Analyses are ongoing to better understand the role of factors such as adherence, drug exposure, and baseline viral load in virological failure,” the researchers stated in their article.

In terms of adverse events (side effects), rilpivirine was more tolerable. Fewer ECHO participants in the rilpivirine arm discontinued the study due to adverse events—eight (2%) taking rilpivirine vs. 27 (8%) on efavirenz. Participants reported significantly less frequent grade 2–4 (moderate to severe) adverse events with rilpivirine than efavirenz (16% vs. 31%, respectively), and rash, dizziness, and abnormal dreams or nightmares were more commonly reported in the efavirenz arm. Increases in lipids—LDL (“bad”) cholesterol and triglycerides—in the blood were significantly smaller in those taking rilpivirine.

In the THRIVE trial, which randomized 340 individuals to each study arm, 86% of participants who took rilpivirine achieved viral load below 50 copies/mL, compared with 82% of those on efavirenz. As in the ECHO trial, however, more people experienced virological failure on rilpivirine than efavirenz (7% compared with 5%).

“Response rates seemed highest in the rilpivirine group for patients with lowest baseline viral loads, and background [treatment] regimen seemed to have no significant effect on responses,” the researchers noted in The Lancet.

Rilpivirine takers and efavirenz users responded comparably well (89% and 90%, respectively) at better than 95% adherence. Those reporting 95% or lower adherence also responded similarly on rilpivirine (64%) and efavirenz (62%).

Fewer rilpivirine takers discontinued the study due to adverse events (4% vs. 7%), and grade 2–4 adverse events were reported by fewer participants in the rilpivirine arm (16%) than in the efavirenz group (31%). Also echoing the ECHO results, cases of rash and dizziness and increases in blood lipids were significantly lower with rilpivirine than with efavirenz.

The THRIVE trial researchers concluded that, despite the higher number of virological failures, “a favorable safety profile and non-inferior efficacy compared with efavirenz means that rilpivirine could be a new treatment option for treatment-naive patients.”

Side Effects Seen in ECHO and THRIVE

The table on page 16 lists the most commonly reported grade 2–4 (moderate to severe) adverse events that emerged following treatment with regimens containing rilpivirine or efavirenz in the ECHO and THRIVE trials. Bear in mind that trial participants were taking a background treatment regimen along with either rilpivirine or efavirenz; therefore the side effects below may be attributable to other drugs.

These percentages indicate that, on the whole, fewer trial participants in the rilpivirine arm experienced moderate to severe adverse events compared with those in the efavirenz arm.

Interestingly, slightly more rilpivirine takers reported depressive disorders, despite efavirenz’s reputation for psychiatric side effects. The incidence of all reported depressive disorders (not just grade 2–4) across both trials was 8% in the rilpivirine arm and 6% in the efavirenz arm. In both arms, 1% of participants discontinued treatment due to depressive disorders.

Pooled 96-Week Analysis

Analyses of pooled (combined) 96-week data from both ECHO and THRIVE confirm rilpivirine’s “non-inferior” efficacy and favorable side effect and lipid profiles compared with efavirenz, but also raise concern over rilpivirine’s efficacy at higher viral loads.

At the 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, held July17–20,
in Rome, Italy, Calvin Cohen of the Community Research Initiative of New England reported that 78% of participants across both study arms in both trials saw their viral load fall below 50 copies/mL at 96 weeks. Virological failures were uncommon after week 48 (3% with rilpivirine and 2% with efavirenz). Among those who did not achieve undetectable viral load or who experienced viral rebound, NNRTI resistance mutations arose in 57% of rilpivirine takers and 54% of participants on efavirenz. Resistance mutations to nucleoside/nucleotide reverse transcriptase inhibitors, however, occurred more frequently upon virological failure among those on rilpivirine than efavirenz (56% compared with 31%).

In terms of safety and tolerability, 96-week results were consistent with 48-week findings. Moderate to severe adverse events remained less frequent with rilpivirine (17%) than efavirenz (33%), and occurrence of these adverse events increased only slightly between weeks 48 and 96 (1% with rilpivirine and 2% with efavirenz); rates of discontinuation due to adverse events were still lower among rilpivirine takers (4% vs. 9%). Rash, dizziness, and abnormal dreams continued to be more common and lipid increases remained greater in those taking efavirenz. There were no new safety concerns between weeks 48 and 96.

**The Complera Combination**

Complera combines rilpivirine with the NRTIs tenofovir (Viread) and emtricitabine (Emtriva)—the two drugs that make up the Truvada pill. It’s not the first to unite “nukes” and “non-nukes” in a single pill: That honor goes to Atripla, which combines tenofovir and emtricitabine with efavirenz. Like Atripla, Complera packs a full regimen into a single pill taken once a day. (These similarities have earned the new combo the nickname “B-tripla.”)

Where Complera and Atripla part ways, however, is in their side effect profiles: Research to date suggests Complera users benefit from rilpivirine’s safety and tolerability. Evidence comes from two studies presented at the 13th European AIDS Conference, held October 12–15, 2011, in Belgrade, Serbia.

**More from ECHO and THRIVE**

All participants in the ECHO trial described above took tenofovir plus emtricitabine in addition to either rilpivirine or efavirenz; this means that participants who were randomized to receive efavirenz were taking the three drugs that make up the Atripla combination pill, and those taking rilpivirine were on Complera. THRIVE participants took either rilpivirine or efavirenz, along with tenofovir/emtricitabine or another single-pill regimen; thus, some participants in THRIVE were taking the Atripla drug combination, others were using Complera, and still others were using regimens not currently available as a fixed-dose tablet.

A pooled analysis of 96-week data from ECHO and THRIVE presented last October includes only data from trial participants who took the Complera or Atripla combinations, allowing researchers to conduct a head-to-head comparison of the two regimens. The analysis revealed that, at week 96, 77% of participants in both treatment arms had achieved a viral load below 50 copies/mL—confirming Complera’s non-inferiority to Atripla for first-line treatment.

“Snapshot analyses” in subgroups of participants showed how well each drug combination worked in people starting treatment at various viral loads. Complera was comparable to Atripla in people who started treatment with fewer than 100,000 copies/mL (83% and 80%, respectively, achieved undetectable viral loads) and in those who started with a viral load below 50 copies/mL—confirming Complera’s non-inferiority to Atripla for first-line treatment.

**Table 1. Percentage of Trial Participants Reporting Grade 2–4 Adverse Events in ECHO and THRIVE**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Rilpivirine + Background ART</th>
<th>Efavirenz + Background ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Headache</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1%</td>
<td>7%</td>
</tr>
<tr>
<td>Depressive disorders*</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Rash</td>
<td>3%</td>
<td>11%</td>
</tr>
</tbody>
</table>

*Defined as experience of depressed mood, depression, dysphoria (sadness or discontent), major (clinically diagnosed) depression, altered mood, negative thoughts, or contemplated or attempted suicide.
Switch Study

Also described at the European AIDS Conference was an open-label study, conducted by Calvin Cohen and colleagues, that assessed the safety and efficacy of switching from Atripla to Complera for people with good viral suppression.

Forty-nine participants switched from Atripla to Complera. All had at least eight weeks of undetectable viral load (below 50 copies/mL) on Atripla before the switch. The primary endpoint of the study was viral suppression 12 weeks after switching regimens.

At week 12, all study participants maintained their undetectable viral load. Blood levels of rilpivirine were comparable to those in ECHO and THRIVE participants who had not taken efavirenz, suggesting that switching to rilpivirine did not dangerously lower drug levels in the body. Only two moderate drug-related adverse events occurred, there were no severe adverse events, and no participants discontinued treatment due to side effects.

Two New Treatment Options— for Whom?

The studies described above indicate that rilpivirine and Complera are comparable to efavirenz and Atripla but cause fewer troublesome side effects. So who is most likely to benefit most from these new treatment options?

Adult First-Timers

First of all, rilpivirine and Complera are currently approved only for adults (age 18 or older) starting their first treatment regimen. Trials completed to date have excluded younger participants, so it is unknown how safe or efficacious these medicines are for people whose bodies are still growing and developing (although an international study is now evaluating rilpivirine in 12-to-18-year-olds).

The switch study described above was reassuring but very small and only looked at the safety and efficacy of switching from an efavirenz-based regimen to Complera. Data to show whether the drugs work as well in or are safe for use by people with prior exposure to antiretroviral drugs are so far extremely limited.

People with Efavirenz Intolerance

Plenty of data do support treatment simplification—simpler, more convenient regimens facilitate adherence, which in turn enables better viral suppression and improved immune function—and Complera’s convenience as a single-pill once-daily regimen is matched only by Atripla. However, fewer rilpivirine users than efavirenz users in clinical trials stopped treatment because of side effects, suggesting that people who opt for Complera may have an easier time sticking with their regimen.

Also, psychiatric side effects associated with efavirenz may give some people pause before choosing Atripla; current or past mental health issues may render it a less suitable option than Complera (although a small number of trial participants taking rilpivirine did report experiencing depressive disorders). Remember, it’s essential to frankly discuss your current health and medical history with your clinician before starting any medication, in order to find the best regimen for you. Not everyone who takes a drug experiences adverse events, but some people may be predis-

CONTRAINDICATIONS

Certain drugs and supplements can affect the way the body processes rilpivirine, leading to low blood levels of rilpivirine and the risk of drug-resistant HIV. Drugs contraindicated for use with rilpivirine-containing regimens include:

- the anticonvulsants oxcarbazepine and phenytoin, used to treat epilepsy and prevent seizures; carbamazepine, used in treatment of epilepsy and bipolar disorder; and phenobarbital, used to treat epilepsy, relieve anxiety, and prevent barbiturate withdrawal symptoms;
- the antimycobacterials rifampin and rifapentine, used primarily to treat tuberculosis, and rifabutin, used in treatment of tuberculosis and Mycobacterium avium complex;
- proton pump inhibitors, such as esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole, which dramatically reduce production of digestive fluid in the stomach;
- more than one dose of the steroid dexamethasone, used to manage inflammatory diseases (such as rheumatoid arthritis) and other conditions; and
- the herbal supplement St. John’s wort, taken to help relieve depression.

If you and your medical team are considering rilpivirine or Complera (or any drug, for that matter!) as part of your HIV-management strategy, it is important to discuss any other medications or alternative treatments you are currently using.

For more about possible drug effects and interactions, see the rilpivirine and Complera prescribing information at www.edurant-info.com/sites/default/files/EDURANT-PI.pdf and www.complera.com/Complera_prescribing_information.pdf.
posed by genetics or non-HIV-related health conditions to experience unwanted—and avoidable—side effects.

**Those Starting with Lower Viral Loads**

The rilpivirine/tenofovir/emtricitabine combination that makes up Complera is listed as an “alternative” NNRTI-based regimen in the current DHHS treatment guidelines (last updated in October 2011).

The guidelines, compiled and updated by a panel of HIV experts and advocates, cite two main reasons for Complera’s secondary status to its fellow NNRTI-based regimen, Atripla: limited data so far on the durability of virological suppression, and lower virological response in people starting treatment with viral loads above 100,000 copies/mL. Based on these research findings, “the panel recommends [rilpivirine/tenofovir/emtricitabine] as an alternative regimen for initial therapy.”

Successfully suppressing viral replication is key to avoiding the development of drug-resistant HIV, including mutations against other drugs within the same class; this was seen with the NNRTI etravirine (Intenence) in the ECHO and THRIVE trials. “Caution should be exercised when using [rilpivirine] in patients with plasma HIV RNA > 100,000 copies/mL,” the guidelines state, “given the higher [rilpivirine] virologic failure rates and the greater probability of [etravirine] resistance at the time of failure observed in this population during clinical trials.”

**Others?**

For many reasons, clinical trial participants are rarely a perfectly representative sample of the populations most likely to use the drug or other intervention being studied. Trials of rilpivirine and Complera are no exception, and plenty of questions remain.

For example, in the switch study described above, 92% of participants were men and 80% were white. Could sex or ethnicity have a hand in the drug’s efficacy, safety, and/or tolerability after switching from an efavirenz-based regimen? A report by BETA contributor Liz Highleyman of HIVandHepatitis.com quotes Calvin Cohen addressing the issue of drug levels and race: Because people of African descent tend to have higher blood levels of efavirenz, he said, they may enjoy an “even longer cushion” of post-switch efavirenz working to suppress HIV.

Also, will rilpivirine be a safe alternative to efavirenz for pregnant women? Animal studies did not show “teratogenic potential”—potential to damage the developing fetus—and the drug is currently classified by the FDA as a “Pregnancy Category B” drug, which means no harm is expected but the drug has been inadequately studied for use by pregnant mothers. The package insert for Complera states that use during pregnancy is acceptable “only if the potential benefit justifies the potential risk.”

**Conclusion**

Clinical trial results to date attest to rilpivirine and Complera’s promise and highlight concerns about less-than-ideal efficacy in some people, especially those starting out with high viral loads. The questions posed above (and others) remain to be answered as clinical trials of rilpivirine-containing regimens continue, and as individuals and their clinicians gain experience using them.

In the meantime, rilpivirine and Complera appear to represent welcome new treatment alternatives for people starting ART for the first time.

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

**Selected Sources**


