TRENDS-in-MEDICINE

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by Lynne Peterson

SUMMARY

- Uptake of Gilead's Stribild is slow but steady, constrained by habit, cost, insurance, satisfaction with Gilead's Complera and Atripla, and concerns that resistance could develop, making patients ineligible for ViiV's dolutegravir.
- Gilead's new-and-improved tenofovir alafenamide fumarate – which is being incorporated in a new Quad pill – appears to have less renal toxicity or effect on bone mineral density, but there is an increase in neutropenia that needs to be watched.
- Zinc finger technology, developed by Sangamo BioSciences to disable the CCR5 and CXCR4 cells that HIV requires to survive, generated a lot of excitement at CROI 2011, but there was no discussion of it this year.
- HCV was a hot topic, and doctors are gearing up for all-oral regimens, including AbbVie's ABT-450/r-based regimens and Gilead's sofosbuvir + ledipasvir, and others. There is no clear winner in this space. An "A" is an "A" is the current thinking, so it may come down to price or marketing.

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CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS (CROI)

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This was the 20th CROI, and it was looking like it would be one of the biggest meetings yet, with 4,252 people registered (none of them exhibitors because there are no exhibitors at this meeting). However, at the last minute an unknown number of National Institutes of Health (NIH) scientists were no-shows. The rumor was that more than 50 NIH researchers were told directly that they could not attend as a result of government sequestration.

Kevin De Cock, MD, director of the Centers for Disease Control and Prevention's (CDC's) Center for Global Health and chairman of the scientific program committee for CROI, said he didn't have a count of how many NIH researchers had to cancel, but he called the situation "unfortunate." Dr. De Cock said the situation has "interesting historical implications…In 1991 there was controversy and subsequent restrictions of travel of U.S. scientists going outside the U.S. for conferences over a concern that this was not the best use of money. And 20 years after we face [a similar problem]…We did hear in the last few days that, following the implementation of sequestration, that a number of government-sponsored investigators did not travel to the conference [CROI]. I don't have at my fingertips the exact number. I think it was handled on an agency-specific basis." Lynne Mofenson, MD, an infectious disease specialist from the National Institute of Child Health and Human Development, NIH, said half of her six-member team had to cancel.

The problem with canceling at the last minute for this meeting (and most medical conferences) is that the registration fee is prepaid and non-refundable, airline tickets are prepaid and usually non-refundable, and the hotels also are often prepaid and non-refundable. So, all NIH saved by not sending the scientists was the daily food allowance and taxi fare to and from the airport. Thus, NIH wasted a lot of money by not sending the people scheduled to attend, suggesting this was a purely political move unlikely to accomplish much to resolve sequestration.

Scott Hammer, MD, an infectious disease specialist from Columbia University College of Physicians & Surgeons and vice chair of the scientific program committee for CROI, said there were five themes at this year's meeting:

- New developments, agents, and formulations in antiretroviral therapy (ART).
- Hepatitis C, which "is an increasing part of this meeting."
- Tuberculosis, which "also is becoming an increasing focus." It has always been a part of CROI, but in the last two years TB talks have been clustered together.

- Eradication of reservoirs and HIV persistence.
- New issues and challenges with pre-exposure HIV prophylaxis (PrEP).

CURRENT HIV DRUGS

Doctors now have a smorgasbord of agents to treat HIV. **Gilead Sciences' Stribild** (tenofovir disoproxil fumarate + emtricitabine + cobicistat + elvitegravir, formerly known as Quad) offers a four-in-one pill (three HIV-active agents plus a booster, thus the Quad nickname). It was approved by the FDA in August 2012, and most – but not all – doctors at CROI are prescribing it, but most also are not in a rush to use it. Rather, they are "migrating" to it.

Doctors described the efficacy of Stribild as comparable to two other Gilead drugs – Complera (emtricitabine + rilpivirine + tenofovir) or Atripla (emtricitabine + efavirenz + tenofovir). And some very large HIV centers are concerned that, at least theoretically, a patient could develop integrase resistance to Stribild and then be ineligible for treatment with ViiV's dolutegravir, about which they are very excited.

What percent of HIV patients are renally impaired and, thus, ineligible for Stribild or Viread (tenofovir dioproxil fumarate)? Doctors estimated it is <15% of patients. David Thomas, MD, director of the Division of Infectious Diseases at Johns Hopkins, said, "As the HIV population gets older, and in a setting where there are a high number of other risk factors, we have a good bit of it…Most clinicians in our setting are pretty attuned to it, but it is less than 10% of patients." Douglas Dieterich, MD, a gastroenterologist from Mount Sinai School of Medicine, added, "It is higher in African Americans and diabetics. It is 10%-20% but getting more common."

Comments on Stribild use and outlook included:

- *California #1 (~220 patients):* "I don't use Stribild in renally-impaired patients, hypertensives, or African Americans. In the VA [Veterans Administration], a majority of our patients are older, so 50% are not even eligible…I use a lot of Atripla, and I don't change patients if they are doing well and are undetectable. I leave them alone as long as they tolerate Atripla. New patients depend on the formulary, but the number of new patients in my practice is ***very*** low… I also use a lot of raltegravir [Merck's Isentress], which is comparable to Stribild, even though raltegravir is BID. Part of that is legacy, I put a lot of patients on it when it came out. There was a lot of enthusiasm for it as a new class…It might be logical to switch patients to Stribild, but people are not doing that if patients are doing well…In one year, I'll probably switch fewer than 10% of my patients to Stribild …But over three years, I'll migrate to Stribild."
- *California #2 (~500 patients):* "I've switched some patients to Stribild, but I'm not putting new patients on it, even though the approval is for new patients. I give it to patients on Atripla or Complera who can't tolerate that, mostly Atripla patients…Most of my protease inhibitor patients are on boosted Reyataz [Bristol-Myers Squibb, atazanavir] or darunavir [Johnson & Johnson's Prezista]. Most of them are doing well…Right now about 1% of my patients are on Stribild, and in a year that will increase to 5%."
- *Texas:* "I don't use Stribild a lot…There are no data on women…My patients have AIDS. They are not like the patients studied in the trials, so I use things I know work…I don't use Complera, but I sometimes use Atripla…I'm interested in nucleoside-sparing drugs."
- *Wisconsin (~350 patients):* "I haven't prescribed any Stribild yet, but I don't see new patients; my partners see the new patients. I don't change existing patients if they are doing well. Every once in a while someone asks about Stribild, but not often. And public clinic patients often don't have the option of Stribild. When Stribild gets rid of the renal toxicity issue, it will get patients to switch."
- *New York #1 (~3,000 patients):* "I've only prescribed Stribild 1-2 times. It is still new. Patients often want a drug with some experience. It is not yet a go-to drug…We have not needed to switch a lot of patients. In choosing between Stribild and Complera, it comes down to experience, not renal toxicity…And I had trouble with insurance coverage of Stribild."
- *New York #2 (~1,500 patients):* "I've prescribed Stribild, but only for deep salvage, not new patients. I've taken people with a complicated BID regimen that I think are failing because they are not compliant and put them on Stribild… Stribild use is slow because Complera already exists, and I didn't expect Complera to be so easy to tolerate. Complera is my go-to for naïve patients because I don't have to worry about renal impairment…I've also had insurance coverage issues with Stribild."
- *New York #3 (~1,500 patients):* "I've prescribed Stribild, and my use is going up, but it is extremely expensive, and we tend to use more protease inhibitors…If you give Stribild, Complera, or Atripla, you need to wait for the genotype to come back, but with a protease inhibitor, I can just start, and protease inhibitor resistance doesn't occur. I also don't have to worry about renal toxicity…But Stribild is a great medication and will get a lot of use. Right now, 2%-3% of my patients are on Stribild, and in a year it will be ~5%…

I'm also worried that patients could develop resistance to Stribild and be ineligible for dolutegravir."

- *New York #4:* "I've change a few patients to Stribild, but a lot of insurance companies don't allow it or you have to have prior approval…Atripla is recommended by the guidelines. It is very potent, the most tried-and-true, and the best choice. Once a patient gets used to the initial adverse events, it is well tolerated…I like boosted protease inhibitors…Of Complera, Stribild, and Atripla, I like Complera best…A couple of years ago, I would have said I would be switching protease inhibitor patients to Complera or Stribild, but boosted protease inhibitors are ***very*** good. My favorite is darunavir."

There were no new data on **ViiV's dolutegravir** at CROI, but doctors were talking about it. Comments included:

- "It might have some interesting properties because of the resistance profile, but only a small number of patients fail integrase inhibitors. Is it superior in efficacy? Probably not …If the efficacy and toxicity profile are similar to Stribild, the choice may come down to price."
- "I like that it is once-a-day, requires no booster, is well tolerated, and seems good. It will be a real competitor to raltegravir, which is more trouble to use than Stribild…I could see a combination of dolutegravir and Epzicom [GlaxoSmithKline, abacavir + lamivudine]."
- "Dolutegravir is very exciting. Approval is anticipated in late 2013 or early 2014…And it is likely to be co-formulated with Epzicom…And it may be co-formulated into a single tablet with Prezista…If they can do that, it would be great …My understanding is that mutations with resistance to raltegravir are not likely to confer resistance to dolutegravir …There isn't the buzz at CROI this year as there was last year."

Generics

Generic efavirenz (Bristol-Myers Squibb's Sustiva) and tenofovir (Gilead's Viread) are on the horizon, and doctors said that also is likely to affect their choice of drug to prescribe. In fact, insurance companies are starting to pay attention to the cost of HIV drugs, and doctors expect there will be more pressure to prescribe generics, even if the regimens are tougher for patients. Comments included:

- "With generics, it will become a payor decision as to what we prescribe. We have not yet reached the point in HIV where we are with statins, where we change year-to-year to whatever is negotiated for the formulary. It is more dangerous to change HIV patients, given resistance, so I don't think we are there yet in HIV."
- "Generics are going to be a problem. We are already getting signs of that. This year for the first time we've been challenged on HIV drugs by insurance companies, which are using all kinds of demands for prior authorization for all kinds of drugs, even Atripla. All of a sudden HIV is on the radar. I think some of this is in advance of the Affordable Care Act next year. They are gearing up to review every little thing you do…We are reduced to having a clerk with a high school education second guess what we prescribe. It is just maddening. I was on the phone last week for 20 minutes over an Atripla prescription. The woman said she was trying to locate a consultant to get approval. She said she would call back. Hours later when she still had not called back, I called again, and I waited another 10 minutes on hold. Eventually, I got approval for one year. If this happens with all my patients, it will be impossible. It will drive me out of practice…Formularies are coming. There will be a mandate to try generics TID first."
- "The insurance industry doesn't care if a patient has to take three pills. There will be a huge push against high cost pills from one company – Gilead…I never had a copay issue until last year, but insurance companies have increased their attention to HIV drugs…Gilead is now offering a copay discount card worth up to $400 a month for Stribild and Complera."

INVESTIGATIONAL HIV DRUGS

GILEAD SCIENCES' tenofovir alafenamide fumarate (GS-7340), a nucleotide analog reverse transcriptase inhibitor (NRTI)

Researchers presented a comparison of two different Quad tablet formulations from a small Phase II study: The approved Stribild vs. a new formulation with an improved version of tenofovir – 25 mg tenofovir alafenamide fumarate (TAF) in lieu of 300 mg tenofovir disproxil fumarate (TDF).

At 25 mg TAF showed increased anti-HIV activity in Phase I, a 7-fold increase in intracellular levels, a 90% decrease in circulating plasma levels, and maybe a lower level in kidney and bone tissue. A 10 mg dose is being used in the "New Quad" because cobicistat boosts TAF levels by ~2.2-fold. Plasma exposure was 91% lower with New Quad.

The study showed no significant efficacy difference between the two quads (though the New Quad was numerically worse by 3.1%), and the virologic response curves were similar but not superimposable over 24 weeks. The other safety parameters looked pretty reasonable.

A key goal with TAF is to reduce or eliminate toxicity, and New Quad did have significantly less negative effect on bone mineral density (BMD) and serum creatinine and lipids, indicating those adverse events (renal toxicity, bone loss, and cholesterol) are much less with New Quad than with Stribild. In particular, there were no cases of renal adverse events or discontinuations reported, and there were no cases of proximal renal tubulopathy with New Quad.

The principal investigator, Andrew Zolopa, MD, an infectious disease specialist from Stanford University School of Medicine, said, "[New Quad] looks safe and perhaps safer [than Stribild] and, virologically speaking, has relatively similar response rates to a standard TDF regimen."

However, there was one worrisome finding in the study – an increase in neutropenia with New Quad. And some adverse events occurred more frequently with New Quad, particularly nausea and fatigue, though the overall incidence of adverse events was the same with both versions of Quad.

As for the neutropenia, Dr. Zolopa said, "It was a small study, but what drove the difference was neutropenia at baseline… Treatment-emergent neutropenia is the same in the two arms. But this needs to be answered in larger Phase III studies… Gilead has done quite an exhaustive job looking at markers… There is quite a raging debate in nephrology on what is the best marker for tubular function in the kidneys…All the markers that have been looked at in the study either look equivalent or actually favor TAF [vs. TDF] – less albumin seen in the urine, less retinol-binding protein…[But] we should still be cautious. We need to follow these early results with a Phase III trial with 800 patients…From my point of view, they've done a good job. The renal markers we look at – creatinine rises were smaller, eGFR was less impacted – so I think, on balance, that what you should take away is that it appears safe for the kidneys …And that is supported by the pharmacokinetic data. We know the kidneys are seeing ~90% less tenofovir with this formulation…So, you might anticipate the overall renal safety profile should be better, and that is what seems to be emerging."

Three patients met the protocol-specified criteria for resistance analysis:

- 1 on New Quad with rebound at Week 24, but no resistance was detected.
- 2 on Stribild, 1 with persistent viremia and NRTI resistance, and 1 with late rebound with no resistance detected.

After the formal presentation, a doctor in the audience questioned why Dr. Zolopa didn't show data on tubular function and other details to confirm a lack of renal toxicity. Dr. Zolopa responded, "There was albumin measured and retinol protein. I didn't have time to show all of those, but they favored TAF…I don't know about uric acid, but I don't think there was any difference. At least other markers seem to favor TAF."

Asked if 10 mg of TAF is likely to inhibit hepatitis B virus (HBV) in co-infected patients, Dr. Zolopa said, "Given the drug levels, I would anticipate it would be inhibitory for HBV."

Asked what percent of patients on treatment don't have an effective regimen, Dr. Zolopa said, "In our practice at Stanford virtually every patient who walks through the door we can offer a fully suppressive regimen. Some may require somewhat more complex regimens than a single tablet a day, but everyone should get viral suppression – if they take the pills…The drugs are quite potent, fairly well tolerated, and increasingly convenient, but it still requires patients to take the pills…At Stanford,we specialize in treatment of highly-resistant patients, and we are able to control them."

Stribild vs. New Quad

Measurement	Stribild n=58	New Quad n=112	p-value
HIV RNA <50 copies/mL			
Primary endpoint: HIV-1 RNA <50 at Week 24	89.7%	86.6%	Nss, p=0.36
C_{trough}	26.6%	17.9%	---
AUC_{tau}	21.9%	14.8%	---
Adverse events			
Any adverse event	81%	81%	---
Nausea	12%	18%	---
Fatigue	9%	12%	---
Upper respiratory tract infection	12%	7%	---
Flatulence	3%	5%	---
Lab abnormalities			
Grade 3-4 lab abnormality	14%	17%	---
LDL elevation	3%	6%	---
Neutropenia	2%	5%	---
Total cholesterol increase	15 mg/dL	31 mg/dL	<0.001
LDL increase	17 mg/dL	4 mg/dL	<0.001
HDL increase	2 mg/dL	6 mg/dL	0.007
Serum creatinine at Week 24	+ 0.12	+ 0.07	0.02
Mean eGFR	– 11.8	– 4.9	0.04
Bone measurements			
BMD of spine	– 2.5%	– 0.8%	0.002
BMD of hip	– 2.0%	– 0.3%	<0.001
Patients with no decrease in BMD of spine	12%	38%	---
Patients with no decrease in BMD of hip	23%	41%	---

So, there isn't a lot of resistance? Dr. Zolopa said, "Not a lot of integrase resistance, but if that is a cornerstone, and you build around that either a protease inhibitor or nucs [nucleosides] or non-nucs, then you can get patients fully suppressed."

Other physician comments about "New Quad" included:

- "If you could give it to people with normal renal function, there would be no reason not to use it."
- "TAF means you can use a lower dose. It will be a foundation for combinations with other agents that were not possible before, like boosted protease inhibitors. And there should be less toxicity. Clearly, there are fewer kidney and bone effects. The fact that it showed even that much creatinine effect in that short a period is very exciting…The neutropenia raises questions about whether it gets inside some human cells and can cause a problem. That is why neutropenia is a concern and needs to be watched."

MERCK's MK-1349, a non-nucleoside reverse transcriptase inhibitor (NNRTI)

Matt Anderson, PhD, director of clinical pharmacology at Merck, reported on the results of a single site (Germany), Phase Ib study of this once-daily, next-generation NNRTI, given as monotherapy for 7 days in 18 ART-naïve HIV males. Two daily doses were tested – 25 mg or 200 mg – which brackets the doses being tested in Phase IIb.

In the Phase Ib study:

- The most common drug-related adverse events were headache and loss of appetite.
- The half-life was 9-16 hours.
- The two doses showed very similar viral load reductions at every time period.

A Phase I PK study in healthy normals (presented at CROI in a poster) found:

- MK-1349 showed "slightly less dose proportional increases in AUC and C_{max} between single doses of 6-1200 mg."
- The half-life was compatible with QD dosing, and the T_{max} is ~1-2 hours.
- There was no meaningful food effect.
- It is cleared primarily through the liver, not the kidney.
- At doses up to 1200 mg, it has generally been well tolerated.
- There were no rash and no significant CNS events, and adverse events (mostly headache and loss of appetite) were generally mild-to-moderate. There were two serious adverse events (1 sarcoidosis, 1 LFT increase), but neither was determined to be drug-related.

Asked how MK-1349 is metabolized, Dr. Anderson said, "We have not [done that study yet]…but CYP3A seems to be the major way."

Asked if there was persistence of the antiviral effect after the drug was discontinued, Dr. Anderson said that wasn't studied yet.

MERCK's Zolinza (vorinostat), a histone deacetylase (HDAC) inhibitor

This suberoylanilide hydroxamic acid (SAHA), which belongs to the larger class of compounds known as HDAC inhibitors, is FDA approved to treat cutaneous T-cell lymphoma (CTCL), and there were some early data suggesting it would be helpful in HIV by getting the virus to come out of hiding so it can be killed. However, Sharon Lewin, PhD, an infectious disease specialist from Australia (and past president of the Australasian Society of HIV Medicine), reported that a multidose study of vorinostat for 14 days, worked to wake up latent HIV in 18 of the 20 patients, and it was safe and "relatively" well tolerated with mild-to-moderate adverse events that were reversible on discontinuation – ***but*** ART did not decrease viral levels.

Basically, vorinostat successfully woke up the virus, but then the virus could not be killed with standard therapy. Dr. Lewin said she is not giving up on HDAC inhibitors in general or vorinostat in particular, but these findings suggest that a higher dose, longer duration of vorinostat is needed, or another drug needs to be added to clear virus, "I think it is a first step rather than the end [for vorinostat]. The first step of more than one dose. In my mind the questions are: Should we be giving more drug – maybe not continuously but intermittently? Should we be giving more potent activators? There are studies of other drugs in the class that are more potent in the laboratory. Will we need some immune booster to clear [the virus]?…That strategy might look more like a shock and kill strategy – shock with an activating agent like vorinostat, and then kill with something like vaccine."

Robert Siliciano, MD, PhD, a molecular biologist from Johns Hopkins University School of Medicine, added, "The hunt now is for agents that turn on the virus without T-cell activation… But the cells don't die and are not well recognized by the immune system in patients on HAART [highly active antiretroviral therapy]. So, it is possible that even if we turn on all

the latent virus, the cells will just sit there and make virus. We have to find a way to make them die."

Asked if the vorinostat turned on any host or housekeeping genes, Dr. Lewin said, "Yes, but we wanted to see if it turned on other viruses…There was no activation of Epstein-Barr or CMV [cytomegalovirus]."

THERAPEUTIC CONCEPTS' cenicriviroc, a CCR5 antagonist

In a 24-week, 143-patient study in treatment-naïve HIV patients, adding this investigational agent in lieu of Sustiva on top of Gilead's Truvada (emtricitabine+ tenofovir) was just as effective, and the regimen was easier for patients to tolerate. Joseph Gathe, MD, a Texas infectious disease specialist, reported:

- 76% of patients getting 100 mg cenicriviroc and 73% getting 200 mg achieved virologic success vs. 71% with Sustiva.
- Treatment discontinuations were lower with cenicriviroc – 12% at 100 mg and 14% at 200 mg vs. 25% of Sustiva patients.
- Cenicriviroc reduced inflammatory markers.
- It was a difficult regimen because patients had to take a number of pills at specific times during the day, but a streamlined regimen is planned for Phase III.

While CROI highlighted these findings at a press conference, doctors at the presentation did not seem very impressed. Amalio Telenti, MD, PhD, a Swiss virologist, said that CCR5 inhibitors require testing to determine whether patients have CCR5 tropic disease before treatment can be started, but he added that the drug might be marketed as managing HIV and immunopathogenesis at the same time, "It's not clear how much will end in hype and how much will be a true benefit."

A Phase III trial is planned, but Dr. Gathe said the dose has not been determined yet.

Other HIV Drugs to Watch

There was no information at CROI on these drugs, but some experts said they look promising.

CYTODYN'S PRO-140, another CCR5 antagonist. This was originally a Progenics Pharmaceuticals drug. It may inhibit resistance to Pfizer's Selzentry (maraviroc). A bivalent version reportedly is in development.

TAIMED BIOLOGICS' ibalizumab (TMB-355). This humanized, biospecific monoclonal antibody has been tested in two formulations – in Phase IIb as an IV infusion and in Phase I as a once-monthly injection. In addition a second-generation formulation with a bispecific antibody-like fusion protein is in preclinical development, with an investigational new drug (IND) application expected to be filed with the FDA this year.

Ibalizumab is being developed with Rockefeller University, but several pharmas reportedly are looking at it.

HEPATITIS C VIRUS (HCV)

HCV took a much more prominent position at CROI this year than in the past. At a press conference on HCV drugs, Dr. Thomas of Johns Hopkins said, "Interferon has been the work-horse of HCV, and we are about to change all that and move from the horse to the automobile. In places where you can get automobiles, you probably won't turn back. This transition is transformative and huge and makes a big difference to patients." Another expert added, "We are in a state of a paradigm shift from interferon to direct-acting antivirals [DAAs]." Another called HCV drug development "HIV drug development at warp speed." In fact, that was the way virtually every expert at the meeting was describing the treatment changes on the horizon.

Asked how they will compare the SVR rate for different all-oral DAAs, some experts said that anything within a 7% difference would be considered comparable, but a European doctor said a 15% differential would be relatively inconsequential. However, the first digit in the SVR rate could be important for even smaller differences than 7% – because 9x% just sounds better than 8x% (so 91% sounds better than 89%).

- *Dr. Dieterich:* "All of the polls of doctors indicate the break point is ~7%. If it is more than 7% better, then people will go the extra mile…[But] we may not be able to use the drugs we want, depending on insurance coverage. That will be a real challenge."
- *Dr. Thomas:* "Another thing to consider is the consequences of failing the first time…If we are looking at a drug with little chance of failure…it may make physicians more apt to try a regimen with more than a 7% difference – if, for example, it was on formulary."
- *Eric Lawitz, MD, medical director at Alamo Medical Research in San Antonio TX:* "There is some psychology in the first digit. If that is a 9 vs. an 8, that may make a difference."

Dr. Dieterich cautioned that the SVR numbers seen in clinical trials will not be replicated in the real world, "It is not the

same in the real world. It won't be 98% or 100% SVR in the real world because the real world is messy, and the patients are sicker in the real world. It is important that you can't promise patients 98% because it won't happen in the real world."

Asked how they will choose among the DAAs, experts agreed it is unlikely to be up to them, that insurance will dictate their first choice, but drug-drug interactions (DDIs) and cost could be issues. One thing they said they didn't consider an issue was pill burden over a 12-week course of therapy. Dr. Dieterich said, "This is not lifelong therapy, so the number of pills doesn't matter." However, one expert warned that it is not necessarily true that more pills mean a higher price; that all depends on pharma pricing decisions.

Juergen Rockstroh, MD, an infectious disease specialist from Germany who moderated the session where the HCV trial data were presented, said, "Cost will be a factor, so will drug-drug interactions. If those are equal, then ritonavir may be a factor."

Dr. Rockstroh cautioned that in comparing the results of combinations from different companies, it is important to remember that the patient populations are not identical. For instance, he said the Gilead data do not include cirrhotics, though in the real world cirrhotics will be a target, "So, [the Gilead interferon-free regimen] did not answer what happens in the most difficult patients…Which patients you select drives SVR…And different drug combinations are likely to be used in different genotypes."

Asked about their attitude toward combinations of two drugs that get approved by the FDA separately but are not labeled for use together, most experts said they would be comfortable doing that if there are adequate safety and efficacy data on each. Dr. Dieterich said, "In the best of all possible worlds, I think, considering what we know about DDIs with HIV medications …we can probably put together a rational regimen that has been studied in at least Phase II…This is not going to be like the old days of HIV where you could just write scripts and have them filled…If there were no insurance companies out there saying not to use that, I would probably be doing it, putting together regimens with approved drugs…and we could argue it is rational in [some] patients." Dr. Thomas said, "We will try to do it before the insurance companies catch on." Dr. Dieterich responded, "I think they are on to us already." Dr. Rockstroh said, "I think people will play with them in the clinic – maybe putting together sofosbuvir from Gilead and TMC-435 [simeprevir] from Johnson & Johnson/Tibotec."

Experts also said they are warehousing patients in anticipation of all-oral DAAs. Dr. Lawitz quipped, "I need a second floor for my warehouse…Certainly, those with mild-to-moderate as timelines and low fibrosis, I would put in a warehouse and wait for approvals." Dr. Dieterich added, "If we don't have to use [Vertex's Incivek (telaprevir) or Merck's Victrelis (boceprevir)] now we don't…but we are still writing prescriptions for people who can't wait."

Will the launch of an interferon-free regimen translate into a flood of new patients? There will initially be a bolus of warehoused patients, but there may be a shortage of doctors because some gastroenterologists have stopped treating HCV. Dr. Lawitz said, "The number of treaters in HCV has gone down with boceprevir and telaprevir – because of drug-drug interactions and complexity. So, we have to re-recruit the doctors who used to use interferon. We have to recruit the physicians who have kind of given up and then increase the treater base." Dr. Dieterich said, "[Interferon-free regimens] will open the floodgates, no doubt. All HIV treaters are chomping at the bit."

What is the status of DDI studies? Edward Gane, MD, a hepatologist from New Zealand, said Gilead did DDI studies of sofosbuvir/RBV, and there were no significant DDIs, and DDIs for ledipasvir are underway and "need to be completed before a fixed dose combination study can begin in co-infected patients." He didn't know when those ledipasvir studies would be done but expected that would be before the end of 2013. Dr. Lawitz said DDI studies of the AbbVie drugs are ongoing.

Asked if he thought patients could get away with a shorter duration of therapy such as 8 weeks, Dr. Gane said "A number of durations are being looked at."

ABBVIE and ENANTA's ABT-450/r, an NS3/4A protease inhibitor

ABT-450 is the backbone of the all-oral regimen that AbbVie is developing. Dr. Lawitz presented the 48-week results from a study of once-daily ABT-450 with ritonavir + ribavirin (RBV) in HCV-1 patients. There were four cohorts in this study – 3 were in treatment-naïve patients (one with the addition of ABT-072, and two with the addition of ABT-333, and one in prior PR non-responders. ABT-072 (which is QD) and ABT-333 (which is BID) are non-nucleoside NS5B polymerase inhibitors.

The study found:

- No virologic breakthroughs on treatment.
- One patient relapsed at post-treatment Week 8 and a second relapsed at post-treatment Week 36.
- SVR24 rates were 86%-95%, including 100% (18 of 18) of IL28B T allele patients.

- ABT-450/r 250/100 mg and 150/100 mg doses showed comparable response rates.
- Among previous non-responders to pegylated interferon + RBV (PR), 47% achieved SVR24.
- All patients who relapsed did so by their first post-treatment visit.
- Relapse after post-treatment Week 12 was infrequent in these studies (1 in 61 or 1.6% of patients).
- There were transient asymptomatic increases in indirect bilirubin, a known side effect of ABT-450. The maximum bilirubin increase was 6.4 mg/dL, but it normalized with continued dosing. There was one patient who discontinued for ALT elevation at Week 2, but that patient did not have bilirubin elevation, and the ALT level normalized upon discontinuation of the drug.

Martin King, PhD, a statistician for AbbVie, presented the results of a 321-patient analysis on the risk of virologic relapses in HCV-1 patients treated with a 5-drug ABT-450 regimen – ABT-450/r + ABT-267 (a once-daily NS5A inhibitor) + ABT-333 + RBV – designed to find the optimal treatment duration.

48-Week Results with Abbott All-Oral Combinations

SVR12	SVR24	Breakthrough	Relapse
Cohort 1: ABT-450/r 150/100 mg QD +ABT-072 400 mg QD + RBV in 11 treatment-naïve patients			
91%	91%	18%	---
Cohort 2: ABT-450/r 250/100 mg QD + ABT-333 400 mg BID + RBV in 19 treatment-naïve patients			
95%	95%	0	---
Cohort 3: ABT 450/r 150/100 mg QD + ABT-333 400 mg BID + RBV in 14 treatment-naïve patients			
93%	86%	0	---
Cohort 4: ABT-450/r 150/100 mg QD + ABT-333 400 mg BID + RBV in 17 non-responders			
47%	47%	35%	18%

Abbott All-Oral Regimen Adverse Events

Adverse event	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Fatigue	27.3%	47.4%	42.9%	35.3%
Nausea	27.3%	21.1%	21.4%	23.5%
Headache	36.4%	26.3%	14.3%	17.6%
Dizziness	9.1%	5.3%	28.6%	23.5%
Insomnia	9.1%	26.3%	21.4%	0
Pruritius	0	21.1%	0	11.8%
Rash	18.2%	21.1%	7.1%	5.9%
Vomiting	9.1%	5.3%	21.4%	0
Dry skin	27.3%	5.3%	0	0

Abbott All-Oral Regimen by IL28B Phenotype

Measurement	CC	CT	TT
SVR24 in treatment-naïve patients	85%	100%	100%
SVR24 in non-responders	---	50%	40%

Dr. King reported that:

- The probability of a relapse for a patient taking these 5 drugs was 1.2% with an 8-week regimen but only 1.0% with a 12-week regimen.
- Treatment duration was significantly associated with relapse, and baseline HCV RNA and genotype were "marginally" associated with relapse, but IL28B genotype was not associated with relapse at all (p=0.5).
- 11 of the 13 patients who relapsed were treated for ≤8 weeks, but adherence did not appear to be a factor since only one of the relapsers had low adherence.

Dr. King concluded that a 12-week regimen is optimal for both treatment-naïve patients and null responders.

It was clear that treatment with ABT-450 requires more drugs than the Gilead regimen will require, perhaps 5 vs. 3, and a slightly more complicated regimen. How does this affect the competitiveness of ABT-450 combinations vs. the Gilead combination? It may all come down to insurance companies, formularies, and cost.

GILEAD SCIENCES

sofosbuvir (GS-7977), a once-daily NS5B nucleotide inhibitor + ledipasvir (GS-5885), an NS5A inhibitor + RBV

The results of the ELECTRON trial were presented by Dr. Gane, the ELECTRON principal investigator, who reported that at 12 weeks sofosbuvir + RBV in HCV-1 patients resulted in SVR12 of:

- 84% in treatment-naïve patients, but adding ledipasvir increased the efficacy to 100%.
- 10% in null responders, but adding ledipasvir increased efficacy to 100%.
- No patients in either group given triple combination therapy relapsed after treatment discontinuation.

While Dr. Gane said there were no additional safety or tolerability issues, it is interesting that the Grade ≥2 adverse events were higher in the treatment-naïve patients than in the null responders, whether ledipasvir was added or not.

ELECTRON Results				
Measurement	Sofosbuvir + RBV		Sofosbuvir + ledipasvir + RBV	
	Treatment -naïve	Null responders	Treatment -naïve	Null responders
Efficacy				
SVR4	88%	10% (yes, 10%)	100%	100%
SVR12	84%	10%	100%	100%
Adverse events				
Serious adverse events	4%	0	8%	0
Grade ≥2 adverse events	40%	30%	48%	22%
Grade 3 lab abnormalities	44%	40%	52%	22%

Sofosbuvir (GS-7977) + RBV

A study of this all-oral doublet therapy in 60 high-risk, inner-city, treatment-naïve HCV-1 patients found that 24 weeks of therapy led to better results with weight-based RBV than low-dose RBV.

- Viral clearance was slower in relapses.
- SVR12 – 68% with weight-based RBV and 48% with low-dose RBV.
- SVR4 – 72% with weight-based RBV and 56% with low-dose RBV.
- There was more decreased hemoglobin and hyperbilirubinemia with weight-based RBV.
- Relapse was associated with low-dose RBV, male gender, and high HCV RNA levels.

BOEHRINGER INGELHEIM's faldaprevir (BI-201335), a once-daily oral NS3/4A protease inhibitor

Dr. Dieterich presented the interim results of the 308-patient Phase III STARTVerso 4 trial at Week 12 in **HIV/HCV co-infected patients**. He called the results "quit encouraging" and "about equal to mono-infected data."

At 12 weeks the study showed:

- Undetectable HCV RNA at Week 4 in 80% of treatment-naïve patients and 91% in prior relapsers.
- Undetectable HCV RNA at Week 12 in 82% of treatment-naïve patients and 91% in prior relapsers.
- End-of-treatment success was observed in 80% of patients, half of whom will stop treatment at Week 24.
- Interim data compared well with early response rates in mono-infected patients.
- Adverse events were comparable in dual-infected patients as in monotherapy patients.

Asked about the lower rate of anemia in this trial vs. some other trials in co-infected patients, Dr. Dieterich said both Epogen (Amgen, epoetin alfa) and RBV dose reductions were allowed in the trial, adding, "But it is a different protease inhibitor than telaprevir or boceprevir…It is once a day…There is a little rash and a little sun-related rash, so all patients got sunscreen…but there was much less with this compound [than with telaprevir]."

Asked about the outlook for this therapy given that interferon-free regimens are around the corner, Dr. Dieterich said, "There are studies ongoing of [this] and a combination of simeprevir (TMC-435) – both with PR. They represent a significant advance over boceprevir and telaprevir…and DDI data with both drugs with HIV medications have been worked out quite well, so we know how to use them in HIV…Since we don't know when the IFN-free regimens will be on the market …and I'm sure these will be tested in IFN-free regimens, in the meantime we are still seeing patients…While I wouldn't treat someone who is quite ill with boceprevir or telaprevir, I might use faldaprevir and TMC-435…It is not over."

Asked if faldaprevir and/or simeprevir will be FDA-approved before IFN-free regimens, Dr. Dieterich said, "Late 2013 and early 2014 will be interesting as to how many drugs get approved and when…These [faldaprevir and simeprevir] are both very practical compounds, way easier and far superior to boceprevir and telaprevir, so I think we can use them for a while until IFN-free combinations are worked out…The simeprevir NDA is going to be submitted very soon – in the next few weeks. I don't know about faldaprevir."

Dr. Dieterich also noted that there may continue to be a place for regimens with PR in co-infected patients at least until studies of non-interferon regimens are completed and successful.

Dr. Rockstroh predicted there will be a window for faldaprevir but a narrow one, "For co-infected patients, faldaprevir has very good early response rates. If Boehringer Ingelheim gets it licensed in early 2014, I would only treat patients with it if they really needed it. If they had low fibrosis, I would still wait. It could have a short window in lieu of boceprevir or telaprevir."

JOHNSON & JOHNSON/TIBOTEC's simeprevir (TMC-435), an NS3/4 protease inhibitor

Dr. Dieterich also presented the interim 24 week results of a study of simeprevir 150 mg QD + pegylated interferon + ribavirin (PR) in HIV/HCV-1 co-infected patients from the open-label, single-arm, international Phase III TMC-435-C212 trial. He reported:

- 77% SVR12 among naïve and relapsed patients.
- 75% SVR12 among patients who met response-guide therapy criteria.
- At Week 24, 64% of null responders had not experienced treatment failure.

From 20%-30% of HIV patients also have HCV, and the numbers rise to 70%-90% in HIV+ injection drug users. Infection with HIV accelerates HCV toward end-stage liver disease. Historically, PR has shown only 27%-40% SVR.

Dr. Lawitz presented the SVR4 results of simeprevir in combination with Gilead's sofosbuvir (GS-7977) ± RBV in HCV-1 null responders in Cohort 1 of the COSMOS trial. He said this is one of the most challenging-to-cure patient populations. The findings included:

- SVR12 was 96% with RBV and 93% without RBV.
- Interestingly, the Kaplan-Meier curves for mean change in HCV RNA Log_{10} were quite literally the same whether RBV was included or not.
- RVR at Week 12 was better with RBV (85.2% vs. 57.1%), but 100% of patients were undetectable at end of treatment even without RBV.
- Two patients relapsed after receiving all study doses – one who was getting RBV and one who wasn't, both within 4 weeks of follow-up.
- 95% of HCV-1a patients achieved SVR8 vs. 100% of HCV-1b patients.
- The most common adverse events were fatigue (~25%), headache, and insomnia. Anemia only occurred in patients getting RBV.
- 1 patient not on RBV had AL >3xULN but was asymptomatic. Bilirubin increases occurred only in patients getting RBV.

TUBERCULOSIS

SANOFI's Priftin (rifapentine)

A study found that a double dose of this drug allows weekly rather than daily treatment for pulmonary tuberculosis, but the duration of therapy remains unchanged at 6 months. Using rifapentine instead of rifampin (the standard therapy for TB) didn't shorten the duration of treatment, but it meant that for four of the six months, patients only had to take the medication once a week instead of daily.

Amina Jindani, MD, from St. George's, University of London, U.K. – who 30 years ago developed the model for looking at the bacterial activity of drugs and the author of a famous paper on this topic – said, "If a drug can be given once-weekly, the implications for patients are enormous."

Dr. Jindani said there have been three previous trials of rifapentine-based regimens (e.g., rifapentine + isoniazid), but the relapse rates in all of them were unacceptably high and some HIV/TB co-infected patients who relapsed had developed rifamycin mono-resistance. Richard Chaisson, MD, an infectious disease specialist and head of Johns Hopkins University's Center for Tuberculosis Research, commented, "In the U.S. 10 years ago we studied weekly rifapentine, and it was inferior, even though there was not a terrible outcome. The FDA approved it anyway, but most clinicians did not feel it was as good [as rifampin]."

This new study was to see if a higher dose of rifapentine would avoid these problems. RIFAQUIN was a multicenter, 18-month, non-inferiority trial conducted in South Africa. There were three arms:

- **Control:** 2 months of ***daily*** ethambutol, isoniazid, rifampicin, and pyrazinamide followed by 4 months of ***daily*** isoniazid and rifampicin.
- **Regimen 1:** 2 months of ***daily*** ethambutol, moxifloxacin, rifampicin, and pyrazinamide followed by 2 months of ***twice weekly*** moxifloxacin and 900 mg rifapentine (a 4-month regimen).
- **Regimen 2:** 2 months of ***daily*** ethambutol, moxifloxacin, rifampicin, and pyrazinamide followed by 4 months of ***once weekly*** moxifloxacin and 1200 mg rifapentine (a 6-month regimen).

The researchers found that the high-dose, six-month regimen was ***non-inferior*** to control, and it was safe and well tolerated. The four-month regimen was safe and well tolerated, but it was significantly ***inferior*** to control in terms of efficacy. With the 4-month regimen, the time to unfavorable

outcome worsened dramatically starting at ~5 months vs. both control and the 6-month regimen.

Rifapentine Regimens			
Measurement	**Control**	**4-month 900 mg**	**6-month 1200 mg**
Primary endpoint favorable by mITT	86%	74% **Inferior**	86% **Met non-inferiority**
Primary endpoint favorable per protocol	95%	83%	96%
Grade 3-4 drug-related adverse event	6 events	6 events	5 events

Asked what the roadblocks are for adoption of higher dose rifapentine, Dr. Jindani said it is mostly cost, "At the moment, it is an expensive drug…but the manufacturer agreed that if we show efficacy, they are prepared to reduce the price of the drug… The only roadblock we see at the moment is the cost. Once the uptake is there, the cost can come down very, very quickly."

Asked why the shorter course was inferior, Dr. Jindani said, "That is very interesting…In theory, it should have been as good if not better than the 6-month regimen. I don't know the answer to that question. It is a puzzle, but it may be related to…the peak concentration."

Asked if they would start treating patients with rifapentine now and decrease use of rifampin, Andreas Diacon, MD, a pulmonologist from South Africa, said change won't be simple, "We have to talk to the people who organize the treatment programs and retrain thousands of nurses with a new treatment protocol… And there will have to be analysis if that is cost-effective, if the public health systems think that it would increase adherence, and whether it makes sense in their setting. If it does, I think it will be done." Dr. Jirdani said, "There are certain groups where this will be very valuable." Martin Boeree, MD, PhD, a Dutch pulmonologist, said, "Although in the individual case, you might consider it, changing the treatment protocol is very complicated…Ten years ago we were prepared to change, and I think everyone gave up hope on a once-weekly regimen. I think that hope has been rekindled with these results…but you don't just start doing it…You follow CDC guidelines…So, it has to be made a recommendation, but I think there is a reasonably good chance that could happen and happen in the foreseeable future."

Rifampin

Dr. Boeree reported on the PanACEA consortium rifampin dose-finding study. Rifampin has been used to treat TB for 40-50 years, but no dose-finding study was ever done before. The researchers suspected the dose of rifampin that has been used historically (10 mg/kg) is too low.

This Phase IIa study tested higher doses in 68 "healthy" TB patients in South Africa – 20 mg/kg, 25 mg/kg, 30 mg/kg, and 35 mg/kg. They found that adverse events were not increased at any dose tested. He said the ultimate goal would be to be able to shorten therapy with higher doses.

Asked if a higher dose will be problematic for HIV/TB co-infected patients taking an integrase inhibitor since a study presented at CROI last year found that the dose of dolutegravir needs to be doubled when given with the current 10 mg/kg dose of rifampin, Dr. Boeree said, "This is something we don't know the answer to, and it is important to know." Dr. Chaisson added, "It is very worrisome …If the amount of enzymes go up as the dose goes up, that would be a very major concern." Dr. Boeree added that there are animal data suggesting the current dose is the maximum effect of rifampin [on integrase inhibitors], but that is something that needs to be tested."

Asked what he would do with rifampin dosing now, Dr. Boeree said he would continue to use 10 mg/kg, "We can't conclude we can use a higher dose…But in the future I think it will progress very fast that we go into higher doses…This was a Phase IIa study, and we have to confirm it in trials."

HIV ERADICATION AND PREVENTION

At the opening session, Daria Hazuda, PhD, vice president of Merck Research Laboratories, reviewed the history of the discovery of integrase inhibitors, outlining the many challenges and obstacles that had to be overcome. The reason for the history lesson was to emphasize the importance of paying attention to biology then and in the future in efforts to develop drugs for HIV eradication, "A fundamental understanding of biology and biochemistry is absolutely critical…There is so much emphasis now on eradication that we have to realize it is really, really early days. We have the first hints it may be possible…[But] it is really early days, and translating those early findings into an approach that will be viable in the long term will require a ***lot*** of work and a lot of attention to the basic science."

In the same vein, Dr. Siliciano talked about the practical issues of eradicating HIV, including:

- The small pool of latently infected cells.
- How to find drugs that reactivate them so they can be eradicated.
- If the latent virus is reactivated, will it die? "We have to figure out how to kill them – and how to measure them in patients."

- PCR "vastly overestimates" the problem because it simply is not accurate at very low levels.

Dr. Siliciano said that mathematical models indicated it will take 2-3 $\log_{10}$ reductions to have a significant delay in rebound after reactivation, though that will be extremely variable from patient to patient, especially because of the difficulties with the assays.

Mother-to-child transmission

NIH's Dr. Mofenson talked about mother-child transmission, saying that currently <200 cases of mother-to-child transmission occur annually in the U.S. vs. 1 in 4 women passing HIV on to their baby in 1982. Today, she said, it is safe for women on HAART to get pregnant, "We have relatively limited data on the safety of being on the drugs at the time of conception, but the available data are reassuring, so, yes, you can be on drugs and get pregnant."

Infant cure?

Deborah Persaud, MD, a pediatric virologist from Johns Hopkins University School of Medicine, reported on what she called the "first well-documented" case of a perinatally infected child being ***cured*** of HIV. The findings, if replicated, would be dramatic, but the implications for the U.S. are minimal. It would mean that 50-200 babies a year who are born HIV-infected would be given therapeutic doses of HAART rather than prophylactic doses. The impact could be broader in other countries where pregnant women do not receive the care they do in the U.S.

What makes this case different is that the baby, who was born five weeks premature, was tested faster than usual. The mother was HIV-positive, but that was not discovered until she was in labor, so she was not on ART.

Normally, the HIV status of an infant is not known for 4-6 weeks, but because this baby was in the hospital, two tests were run immediately and within 31 hours, a diagnosis of HIV was confirmed, with a viral load of 20,000 copies/mL, which is low for a baby but a level at which treatment is started in non-newborns.

The doctor then treated the baby with AZT (zidovudine), 3TC (lamivudine), and a therapeutic level of nevirapine. The child became undetectable and remained that way for 18 months, when the child was lost to follow-up. At 23 months, the child's caretaker brought the child back in, saying that the ART had been discontinued at 18 months. Testing found that the child was still undetectable, and a repeat test also showed undetectable levels of virus. At 28 months, the child remains undetectable, leading the researchers to declare that the child has had a "functional cure."

Dr. Persaud said, "We believe very early use of ART prevented formation of memory T cells." In essence, she believes the early treatment prevented any hidden reservoirs of virus from forming.

Asked about prior cases dating back to 1995 of babies spontaneously clearing the virus, Dr. Persaud said, "Ninety-nine percent of those cases were attributed to lab mishaps or contamination… It may [occur at] very, very low frequency…[but] since then there have not been any additional reports."

Asked if it is possible the virus would have disappeared on its own, without treatment, Dr. Persaud said, "That would be a very, very rare outcome…This could be like the Berlin patient [who was cured]."

It is likely that this case will get a lot of media attention, but there was also a lot of skepticism that this really was a cure.

HIV-positive controllers

HIV+ controllers are people who are infected but maintain low levels of virus without therapy. Hiroyu Hatano, MD, an infectious disease specialist from the University of California, San Francisco, reported on a study of 16 HIV+ controllers who were treated with raltegravir + Truvada (Gilead Sciences, tenofovir + emtricitabine) for 24 weeks. The researchers found that HIV RNA levels and rectal RNA levels (by biopsy) went down, suggesting, as expected, that there is ongoing viral replication in the blood and gut of these patients.

The question is whether this category of patients would be willing to go on therapy. Dr. Hatano said the majority of the trial patients continued on therapy >24 weeks.

Shortly after CROI, French researchers reported that ***very*** early (and effective) HIV therapy may, in a small number of patients, lead to a "functional" cure. The results of the VISCONTI trial were published in ***PLOS Pathogens***, showing that 14 patients treated within the first two months of HIV infection were later able to stop antiretroviral therapy without an HIV rebound.

These 14 patients (10 men and 4 women) took antiretroviral drugs for an average of just over 3 years before stopping. All still have HIV, but their viral level is undetectable by standard methods and appears under control without further drug therapy. *Are they functional cures or HIV+ controllers?*