Trends-in-Medicine

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by Lynne Peterson

SUMMARY

♦ 21% of HIV+ people are unidentified – more commonly African Americans and Latinos – and testing designed to help identify them is picking up, but slowly. ♦ Evidence is building that treating HIV patients earlier, when their CD4 count is ~500, is beneficial, but experts do not expect guidelines to change until there are more definitive data. ♦ Data continue to suggest that there is an increased risk of heart attack with GSK's Ziagen (abacavir). ♦ Neuro-cognitive impairment has reared its head again in HIV, and experts are urging that the choice of antiretroviral therapy be based, at least in part, on a new standard –a drug's ability to penetrate the blood brain barrier. ♦ Doctors are very enthusiastic about integrase inhibitors, but a trial of switching patients stable on Abbott's Kaletra to Merck's Isentress failed to show non-inferiority. ♦ Data show definitively that IL-2 is not beneficial in HIV. ♦ Doctors are excited about a potential replacement for new PK boosters such as Gilead's GS-9350 and Sequoia Pharmaceuticals' SPI-452 to replace Abbott's Norvir.

Trends-in-Medicine
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CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS (CROI)

Montreal, Canada
February 8-11, 2009

CROI is the premier scientific meeting in the area of HIV/AIDS and opportunistic infections. Among the hot topics at CROI this year were a number of unanswered questions:

- When should HIV therapy be initiated?
- How can the 21% of HIV-infected patients who have not been diagnosed be identified?
- What is the cardiovascular risk with antiretroviral therapies, particularly GlaxoSmithKline's Ziagen (abacavir)?
- To reduce or prevent neurocognitive impairment, should treatments be chosen based on their ability to cross the blood brain barrier?

Doctors were also interested in new data on residual viremia; Merck's integrase inhibitor, Isentress (raltegravir), which failed a switching trial in patients stable on Abbott's Kaletra (lopinavir + ritonavir); pharmacokinetic (PK) enhancers to replace Abbott's Norvir (ritonavir); and the failure of IL-2 (Novartis's Proleukin) to show a clinical benefit in two long-term trials.

John Coffin, PhD, of Tufts University, the CROI vice chair for basic science, said the only new class of drugs on the horizon that he thinks looks particularly promising is the LEDGF interaction inhibitors, but they are very, very early, and there were no real data on them at the meeting. Dr. John Mellors, chief of infectious diseases at the University of Pittsburgh School of Medicine and CROI science program chairman, highlighted:

- **Vaginal gel.** He called the data "tantalizing" from a Phase II/IIb trial in the U.S. and Africa of Endo Pharmaceuticals/Indevus's PRO 2000, a vaginal gel to prevent HIV infection. The data from the HPTN-035 trial suggest that women adhered well to use of the gel and that it had a protective effect. Indevus has already initiated a Phase III trial.
- **Resurrection of vaccine development.** After the STEP trial failed, Dr. Mellors said the field had gone "back to the basics," but he added that there is "exciting new information" suggesting there may be a future for T-cell vaccines after all.
- **HIV transmission.** Stepwise success is being made in understanding how to optimize prevention of transmission of HIV from mother to child and how best to treat the mother when she needs therapy, even if she had received a single dose of Roxane's Viramune (nevirapine) earlier.
- **Cure.** Apparently the idea of a cure for HIV is "back on the table."

HIV Treatment Outlook

Over the next year – and over the next five years – doctors predicted that the number of HIV patients on therapy would increase, but they insisted it would increase gradually but steadily, not sharply. Dr. Mellors said, "Success will breed more therapy. The greater funding – with PEPFAR (the President's Emergency Plan for AIDS Relief, an international health initiative) – and mounting evidence that earlier treatment is better will push us to increase the number of individuals on treatment. That is the trend. But everyone should recognize that it is not going to be a steady march toward victory. There will be some setbacks. One of those that is looming is drug resistance. I think we agree that with more therapy rolled out, we will see more drug resistance. That is the bad news. The good news is that drug resistance is declining very rapidly in the U.S. because therapy is becoming more effective, easier to take, and more potent. But we all know the therapies used outside the U.S., Europe, and second tier nations are not the optimal therapy, so there will be more resistance to those regimens. It is an economic issue, but we are pushing hard to change that."

Guide to HIV Drugs

Brand name	Generic name	Acronym	Manufacturer	Class
FDA-approved				
Agenerase	Amprenavir	APV	GlaxoSmithKline	PI
Aptivus	Tipranavir	TPV	Boehringer Ingelheim	PI
Atripla	efavirenz + emtricitabine + tenofovir	---	Gilead/Bristol-Myers Squibb	NNRTI + 2NRTIs
Combivir	Lamivudine + zidovudine	AZT/3TC	GlaxoSmithKline	NRTI
Crixivan	Indinavir	IDV	Merck	PI
Emtriva	Emtricitabine	FTC	Gilead	NRTI
Epivir	Lamivudine	3TC	GlaxoSmithKline	NRTI
Epzicom	Abacavir + lamivudine	---	GlaxoSmithKline	NRTI
Fortovase	Saquinavir	SQV	Roche	PI
Fuzeon	Enfuvirtide	T-20	Roche/Trimeris	Entry Inhibitor
Hivid	Zalcitabine	DdC	Roche	NRTI
Intelence	Etravirine (TMC-125)	---	Johnson & Johnson/Tibotec	NNRTI
Invirase	Saquinavir	SQV	Roche	PI
Isentress	Raltegravir (MK-0518)	RAL	Merck	Integrase inhibitor
Kaletra	Lopinavir + ritonavir	LPV/r	Abbott	PI
Norvir	Ritonavir	RTV/r	Abbott	PI
Prezista	Darunavir	DRV	Johnson & Johnson/Tibotec	PI
Rescriptor	Delavirdine	DLV	Pfizer/Agouron	NNRTI
Retrovir	Zidovudine	AZT, ZDV	GlaxoSmithKline	NRTI
Reyataz	Atazanavir	ATV	Bristol-Myers Squibb	PI
Selzentry	Miraviroc	---	Pfizer	CCR5 inhibitor
Sustiva	Efavirenz	EFZ, EFV	Bristol-Myers Squibb	NNRTI
Trizivir	Abacavir + zidovudine + lamivudine	TZV	GlaxoSmithKline	NRTI
Truvada	emtricitabine + tenofovir	TVD	Gilead	NRTI
Videx	Didanosine	DDI	Bristol-Myers Squibb	NRTI
Viracept	Nelfinavir	NFV	Pfizer/Agouron	PI
Viramune	Nevirapine	NVP	Roxane	NNRTI
Viread	Tenofovir	TDF	Gilead	NRTI
Zerit	Stavudine	d4T	Bristol-Myers Squibb	NRTI
Ziagen	Abacavir	ABC	GlaxoSmithKline	NRTI
In development				
---	Elvitegravir	---	Gilead	Integrase inhibitor
---	GS-9350	---	Gilead	PK enhancer
---	GSK-1349572	---	GlaxoSmithKline	QD integrase inhibitor
---	RDEA-427	---	Ardea Biosciences	NNRTI
---	RDEA-806	---	Ardea Biosciences	NNRTI
---	Rilpivirine (TMC-278)		Johnson & Johnson/Tibotec	NNRTI
---	SB-728-T	---	Sangamo BioSciences	CCR5-ZFP
---	SPI-452	---	Sequoia Pharmaceuticals	PK enhancer

Asked how the current economic situation is impacting HIV treatment, doctors said:

- *Massachusetts:* "I hope there will be significant money in the economic stimulus bill currently being discussed in Congress, but I suspect the economy will have a negative impact on treatment."
- *Arizona:* "I haven't seen any impact yet, but we see a lot of Medicaid patients, so we could. Ryan White funding has not increased for the last several years, and I don't expect an increase this year. We have had to restrict our formulary – not getting rid of antiretrovirals but eliminating non-direct HIV medications like anti-hypertensive, diabetic, or psychiatric medications for HIV patients."
- *New York:* "In New York, we are all very concerned this may be an area where budgets will be cut. And we don't expect an increase in Ryan White funding this year."
- *South Carolina:* "Our university budget was cut 25% in July 2008, but HIV wasn't changed. However, it is clear that a lot of grants are in jeopardy. We had a 500-patient waiting list three years ago, but we got rid of it, and now money is being fought over, and we may lose it. Down the road, insurers will put pressure on patients to go to more generic drugs. For now, I'm surviving because a large percent of my funding is through grants, but the future is uncertain."
- *California:* "The first impact will be on the availability of HIV providers. So far ADAP (AIDS Drug Assistance Programs) hasn't changed. We haven't had any impact yet."
- *Canada:* "We have a freeze on new drugs in my province while they get reviewed. I expect a tsunami of evaluation of healthcare spending to be sure the money that is spent is cost-effective. Research funding may be okay."
- *Arizona:* "Our population has been increasing, but there has been a flux (loss) of undocumented workers. We are currently maxed out on Ryan White funding."

What's the pricing environment? Doctors expect more pressure on pricing and tougher negotiation by states and ADAP, which negotiates pricing on a national level.

Having HIV is, in and of itself, a cardiovascular (CV) risk factor equivalent to having diabetes, Dr. Carl Grunfeld of the University of California, San Francisco, reported at CROI. He said, "My prediction is the effect of HIV can't be accounted for by viral load, but we don't have that analysis finished yet …I would urge people taking care of HIV patients to modify the modifiable risk factors."

What should doctors do now when treating HIV, knowing that HIV is a powerful risk factor for atherosclerosis? Dr. Scott Letendre of the University of California, San Diego, said, "The findings mean that we should not only start patients on treatment early but also choose regimens less linked to cardiovascular disease...We will have to pay more attention to a patient's risk factors." Dr. Gary Rubin, a primary care physician from the University of Toronto, Canada, said, "It is time to take cardiovascular risk factors more seriously in HIV patients and begin modifying them earlier." Dr. Alex Klein from Mt. Sinai Hospital in Toronto, Canada, said, "Doctors should do their job and manage cardiovascular risk and assimilate the new risk factors into our approach."

When to Initiate Antiretroviral Therapy

Current U.S. guidelines by the International AIDS Society-USA Panel recommend starting treatment in asymptomatic patients before CD4 T-cell counts are <350 per mm^3, though the guidelines removed a warning against starting therapy if a patient's count was >500. However, some researchers believe mortality can be reduced in asymptomatic patients by starting treatment earlier, even at a CD4 count >500. There were data at CROI both supporting and refuting this position.

In favor of earlier treatment. Dr. Mari Kitahata of the University of Washington presented new results from the large, ongoing NA-ACCORD study, sponsored by the National Institutes of Health (NIH), which found that patients who deferred therapy – even with CD4 levels ≥500 – had a 60% increase in the risk of death from any cause vs. patients who started treatment at that level.

Instead of looking at progression to AIDS or death, the NA-ACCORD researchers looked at all-cause mortality. To Dr. Kitahata, delay means death, based on "robust" evidence of outcomes in more than 9,000 patients followed over a 10-year period. In NA-ACCORD 2,620 people who started HAART (highly active antiretroviral therapy) with a CD4 cell count >500 were compared with 6,553 patients who had similar CD4 counts but chose to defer therapy. After adjusting for a range of possible confounding factors, the odds ratio for death from any cause among those who deferred therapy was 1.6 ($p<0.001$). Dr. Kitahata said, "Our findings suggest earlier treatment could significantly prolong survival…I think NA-ACCORD will change practice to initiate HAART earlier."

Dr. Kitahata also argued that this earlier treatment approach is better because of recent studies showing that HIV infection worsens the outcomes of many illnesses not traditionally associated with the virus, such as cardiovascular disease. Dr. Mellors said this study adds impetus to early treatment. He said that, out of a fear of toxicity, doctors have stayed close to the "edge of the precipice," the lowest possible CD4 count that could go untreated, "Now, I sense – and I think it's the right thing – that we are going to be moving away from that."

500 is too high. However, a European study supported by the U.K. Medical Research Council analyzed 7 cohort studies and did not find a reduction in excess mortality with initiation of treatment above 350. Jonathan Sterne, PhD, of the University

Comparison of Deferring HAART to a Lower CD4 Range vs. Starting with a Higher CD4 Range

Higher CD4 range	Lower CD4 range	Hazard ratio
451 - 550	351 - 450	0.99
426 – 525	326 – 425	1.12
401 – 500	301 – 400	1.09
376 – 475	276 – 375	1.19
351 – 450	251 – 350	1.28
326 – 425	226 – 325	1.21
301 – 400	201 – 300	1.34
276 – 375	176 – 275	1.59
251 – 350	151 – 250	1.71
226 – 325	126 – 225	2.01
201 – 300	101 – 200	2.21
176 – 275	76 – 175	2.61
151 – 250	51 – 150	2.59
126 – 225	26 – 125	2.88
101 – 200	0 - 100	3.35

of Bristol, U.K., and colleagues looked at patients in 15 European cohorts and asked what happened to patients who started HAART with different CD4 cell levels. While there was a clear risk gradient, Dr. Sterne said, "<250 was clearly associated with increased rates of AIDS and mortality. We found some evidence of benefit from starting >350, but the effects on mortality were less dramatic, and there was no benefit from starting >400."

The future. *Which study is most convincing?* They are not identical studies, and each has pros and cons. The European study only looked at patients after they started therapy and used statistical methods to try to account for lead-in time between diagnosis and treatment and to adjust for unknown factors, while Dr. Kitahata's study looked at patients from the moment of diagnosis, eliminating what she called "lead-in bias."

Will guidelines be changed again, this time to a cutoff of 500? It's possible, but most experts refused to predict what the guidelines committees would do. Dr. Mellors said only, "The guidelines committees work in mysterious ways." Clinicians offered different outlooks. Most sources agreed there is not a bolus of patients >500 or even >350 who are likely to get treated right away, though most believe that the number of patients in treatment will increase over the next year as a result of the NA-ACCORD study. The biggest problem, several sources pointed out, is getting the message to patients to come in for diagnosis and treatment early enough, and they said that will take a big education effort.

Physician reaction. Physicians do not expect the guidelines to be changed to 500 without more definitive data. Doctors also do not have a backlog or bolus of patients in their practice who have CD4 around 500, who are not on treatment yet, and who are likely to get treatment this year. For a 500 guideline to significantly boost the number of patients on treatment, doctors agreed that screening will have to substantially increase because that is where those patients will come from. Comments included:

- "NA-ACCORD will definitely affect what I tell patients. That data will be very critical. And the number of patients on treatment will increase...NA-ACCORD also may increase testing."
- "A lot of patients are not anywhere near 500. By the time we see patients, their CD4 count is much lower than that. If testing catches people earlier, then there will be more people around 500, but that will take time. I consider strongly starting therapy at 350, and I'm willing to treat patients higher if they are willing to accept the therapy, but you have to have patient buy-in…I don't think guidelines will change yet. The evidence is still mixed on 500."
- "I don't see the guidelines changing to 500. There is still too much uncertainty about 500."
- "I'm not convinced about 500, but the idea is generally right. Most physicians would treat themselves earlier than they treat patients. But I don't think guidelines will change yet…The START trial will begin to answer the question of whether <500 or >500 makes a real difference."
- "I won't start patients at 500 without a controlled study… The new guidelines (in 2008) are really, really good."
- "We are not seeing a lot of people with early infection (~500). There is no backlog or bolus of patients waiting for treatment at that level."
- "Of our diagnosed patients, 75% are on treatment, 8% are on a patient-determined holiday, and 17% are untreated. We are softening them up, trying to get them started on treatment. About 8% might start if the guidelines were changed to 500. Without that, in one year, we expect 80% to be on treatment; some fence-sitters will go on treatment, and some patients will reach the threshold… START is very expensive, very large, and very controversial. It will take money from individual grants."

RESIDUAL VIREMIA

In a discussion with reporters and in his Bernard Fields lecture at CROI, Dr. Robert Siliciano from Johns Hopkins University School of Medicine, said there are two reservoirs of HIV virus even in patients with undetectable viral load. By studying patients whose viral load had become undetectable – using highly sensitive new assays – researchers found at least some of the residual viremia, and they drew several conclusions about future therapies.

A debate has been raging as to which of the following is responsible for the residual viremia:

a. **Continuous replication of the virus due to inadequate control of replication by the drug therapy.** Dr. Siliciano

pointed out that the arguments in favor of this explanation are invalid:

- **No viral evolution in some patients.** However, Dr. Siliciano said that if you work hard and clone the viruses below 50 copies/mL, you don't see any evidence of new resistance mutations, which he said, "means you can have viremia without viral evolution …Residual viremia is dominated by a small number of clones."
- **Latent reservoir does not decay.** He said there doesn't appear to be any significant replenishment of the reservoir by ongoing replication, making it intrinsically stable.

b. Release of virus from stable reservoirs in the body. Dr. Siliciano argued that this is the correct explanation. He also believes there are two stable reservoirs – one CD4+ memory T-cells and the other unknown but suspected to be progenitor cells.

Dr. Siliciano also explained:

- **HAART can't eradicate the virus.** HAART takes viremia down to the limit of current assays (50 copies/mL), but eradication depends on the infected cell population that turns over the most slowly – and that is a population of cells that decays very slowly, requiring 73.4 years, on average, to eradicate just 10^6 cells. So, HAART cannot eradicate the virus.
- **The HIV virus doesn't replicate in resting CD4 cells**, but activated cells can become infected during the process of going back into the resting state. If a cell became activated again in the future, it could generate virus.
- **Infected memory cells are rare even in the reservoir.** Only 1 in 1 million resting memory cells harbors this latent virus.
- **Much of the residual viremia is coming from an unidentified reservoir.** Dr. Siliciano said, "In about half the patients analyzed, more than half the residual viremia is coming from this alternative source, but in other patients we don't see this…It is extremely difficult to do these studies because the average level is about 1 virus particle per milliliter of plasma…So, it is extraordinarily hard to collect the viruses and analyze them…In about half the patients the residual viremia is dominated by this alternative source."
- **The "mystery" reservoir may be infection of monocyte progenitor cells in macrophage lineage.** Dr. Coffin called the mystery reservoir "one of the most exciting things I've heard…What we found was that if you follow and detail what goes on in undetectable patients over long-term, you find persistent viremia decreases and then levels off. We ***speculate*** that this virus that seems not to go away may be concordant with what Dr. Siliciano is seeing…We see a population of virus in patients treated long-term that doesn't decay, that is stable, which means there has to be a low rate of cell replications, not virus replication. We speculate that there is a small population of cells that can continue to express virus…It is devilishly hard to study this because the number of cells is so small."
- **Intensifying therapy or adding a fourth drug to get viremia down does not work.** Dr. Siliciano said, "Intensification has no effect on residual viremia…This means we have reached the limit of antiretroviral therapy. We will never reduce (viral load) lower with ART (antiretroviral therapy)…(But) we can do a better job of choosing drug regimens and choosing salvage regimens by knowing how much replication there is in the patient and how much each drug contributes to the reduction in replication." There was also an absence of resistance in the reservoirs. He concluded, "We have reached the limit of HAART. We will never lower the residual viremia with antiretroviral drugs."
- **Treatment now needs to be directed at finding the reservoirs and eliminating them.** The first step was stopping the body from replicating the HIV virus, and Dr. Siliciano said, "I would say that step is accomplished. Now, what remains to be done, and what may be harder is to find the stable reservoirs and find ways to eliminate them, and there is a lot of momentum to do that."
- **Therapy probably should be started early.** Dr. Siliciano said, "It is possible by catching people very early we may reduce reservoirs, and waiting may increase the (reservoir) size a little."

Given this discovery, Dr. Siliciano contends that new drugs and drug regimens should be evaluated on their inhibitory potential. He offered a complicated formula for assessing drug activity, which basically found that a drug must lower viral load by 6 logs to be effective. He said, "We don't know how to compute the total inhibitory potential for drug combinations. This is a controversial area in pharmacology…It is the beginning of a more rational choice of regimen (particularly in salvage therapy)."

UNDIAGNOSED HIV PATIENTS AND TESTING

The Centers for Disease Control and Prevention (CDC) estimates that in 2006 21% of HIV patients were undiagnosed, down from 25% of patients in 2003, while the number of patients diagnosed with HIV rose, from 1 million to 1.1 million in the same period. With 56,000 new cases of HIV diagnosed each year, the total number of undiagnosed patients dropped only slightly during that 3-year period – from 250,000 in 2003 to 232,700 in 2006.

At CROI, the CDC provided new information on the patients who make up the undiagnosed HIV population:

- 18.8% of whites infected with HIV are undiagnosed. That's 42.2 per 100,000 people.

- 21.6% of Latinos, or 126.4 per 100,000 people, infected with HIV are undiagnosed. Three times more Latinos than whites are undiagnosed.
- 22.6% of African Americans infected with HIV are undiagnosed. That's 380.3 out of every 100,000 people. Nine times more African Americans than whites are undiagnosed.
- There is no significant difference by sex.
- 26.7% of heterosexual men with HIV are undiagnosed. However, this accounts for 53.7% of all undiagnosed cases.
- 23.5% of men who have sex with men have HIV but are undiagnosed.
- Injection-drug users are the least likely to be undiagnosed: 14.5% of men and 13.7% of women.

Why are so many patients undiagnosed? Michael Campsmith, DDS, a CDC epidemiologist, said, "If you have groups without access to testing, a lack of resources, maybe unstable housing situations, those are big areas to overcome. These are complex issues. Trying to change behavior is not easy…and this (effort) has suffered some from fatigue. It is not on the front page the way it was 25 years ago. The economic climate today is not robust, so people are really trying to stay close with resources and efforts. It is an issue that needs attention, but it is out there competing with a lot of other issues."

What's needed to identify these missing patients now that the low hanging fruit have been identified? Dr. Campsmith said two things:

1. **Updating the compendium of proven prevention activities.**
2. **Making testing more routine.**

In 2006, the CDC recommended that doctors no longer be required to obtain written permission from a patient to do HIV testing (the so-called 'opt-out') approach, allowing doctors and hospitals to routinely screen all patients for HIV. At that time, 20 states were requiring written consent. Currently, only 9 states still have a written consent requirement: Connecticut, Hawaii, Massachusetts, Michigan, Nebraska, New York, Pennsylvania, Rhode Island, and Wisconsin. In all but two of these states (Connecticut and Michigan) opt-out legislation was introduced but failed on the first attempt.

Who is paying for HIV screening tests? While insurance companies in all states pay for HIV ***diagnostic tests***, only California mandates that all insurers in the state pay for HIV ***screening***. The District of Columbia has introduced legislation similar to California's mandate. Existing CDC programs also pay for some screening. In 2007, CDC provided $35 million specifically to expand testing in 25 U.S. jurisdictions with the highest AIDS case rates among African Americans. However, Dr. Bernard Branson, associate director for lab diagnostics at the CDC, said screening is increasingly being paid for by third party insurers, "A number of insurers, including Aetna and United Healthcare announced in policy guidance that they will reimburse for screening, and several Blue Cross/Blue Shields are paying for it on a state-by-state basis."

Clinicians are concerned that testing efforts will be impacted by the current economic situation. The CDC hopes this doesn't happen. Dr. Branson said, "The one place where there is consistent economic growth is healthcare…(Studies have shown that) expanding HIV testing down even to low prevalence was more cost effective than many other health interventions that we did. It has been shown that a person who knows they are infected are 3.5 times less likely to transmit HIV than an infected person who is unaware that he/she is infected…so the long-term consequence (of screening) would be to decrease the number of (HIV) cases." Other comments included:

- *Arizona:* "We just changed the law in Arizona. Written consent is no longer required, and there is no pre- and post-counseling mandate. But our hospital hasn't changed its by-laws yet. Then, we need to get the ER doctors comfortable with testing, especially with rapid testing, but we need money to do that. I want to do a trial of rapid testing in the ER and see if we get the 1% positives that CDC says we should expect and which would make it worthwhile to do the testing. And we want to see how hard the testing is. We also need nurse buy-in as well. People are also afraid of what to do if someone is positive, so we have to set up a consult system."
- *South Carolina:* "No jail in South Carolina tests. South Carolina does not require written consent, but the ERs are not testing yet for financial and ethical reasons. What we need to do is test everyone who comes in – and have insurance pay for the $7 test."
- *California:* "Testing is happening without funding at a time when resources are contracting. People are enthusiastic about testing, but there has to be a way to pay for it."

Will the number of patients in treatment increase over the next five years? Sources all predicted that they would, for a variety of reasons, including:

- **Increased screening efforts.** This is expected to result in slow, steady growth of patients on-treatment. Even if states pass opt-out legislation, there are still other hurdles to overcome. Dr. Branson pointed out, "Not all patients who are diagnosed will need immediate treatment, and it will take some time to continue to diagnose people. I can't think of any endeavor that will identify all 232,700 patients in a single year, so we anticipate this diagnosis of the undiagnosed will be an incremental process…As with measles, it was easy to get the first 60% vaccinated, and then the next 20% were a little more difficult, and then the remaining 20% were much more difficult."
- **Better, more tolerable therapies.** More patients will be willing to start therapy and start earlier with easier regimens and lower toxicity.

- **Increasing evidence that treating earlier is better.** Even if guidelines are not changed to specify that patients should be treated when their CD4 count drops below 500 (currently 350), there is a growing belief that therapy should be started as soon as patients agree. However, there is no bolus of patients in doctors' practices that will suddenly boost the pool of on-treatment patients this year.

MI Risk in Patients on Antiretroviral Therapy

A debate also continues to rage over the risk of myocardial infraction (MI) in patients on an NRTI, NNRTI, or PI. At the heart of this debate is GlaxoSmithKline's Ziagen (abacavir). The D:A:D study last year found a relative risk of 1.94 with abacavir. Then, the SMART study, which was presented in August 2008 at the International AIDS Conference in Mexico City, found a 4.3 HR with abacavir.

D:A:D trial. At CROI, new data from the 30,000-patient D:A:D trial were presented, confirming the previous D:A:D finding that abacavir has an excess MI risk both short-term and long-term. Dr. Jens Lundgren from the University of Copenhagen, Denmark, said, "There was a suggestion the (MI) signal for abacavir is exacerbated by the longer you are on the drug…The longer a patient is on abacavir after 1 year, the stronger the problem becomes…The abacavir problem is immediate, and the risk goes back to baseline when the drug is stopped."

Asked what the D:A:D findings mean for abacavir use, Dr. Lundgren urged "caution" in the use of abacavir, but he didn't tell doctors never to use it.

Abacavir wasn't the only antiretroviral that raised the MI risk in D:A:D. Merck's Crixivan (indinavir), Bristol-Myers Squibb's Videx (didanosine, DDI), and Abbott's Kaletra also had an increased risk of MI, though not as high as abacavir. None of the other antiretrovirals, including tenofovir, were associated with an increased risk of MI.

ANRS trial. However, the French ANRS study found an increased MI risk with abacavir only early in treatment, not long-term. Dominique Costagliola, PhD, from the University of Pierre and Marie Cure in Paris and colleagues looked at patients in the French Hospital Database from January 2000 to December 2006 who had a first MI prospectively reported (definite or probable by European Society of Cardiology definition). In this nested case-control study, they found 289 MI cases and compared them to 884 controls.

Dr. Costagliola found:

- Only ***early*** exposure to abacavir was associated with an increased risk of MI.
- There was a trend towards an increased risk of MI by cumulative exposure to AZT and to d4T.
- All PIs studied except saquinavir had an increased risk, with a statistically significant increase for Kaletra and GlaxoSmithKline's Agenerase (amprenavir) + ritonavir.

Odds Ratio (OR) of Having an MI

Drug	OR
Abacavir	1.08
DDI	0.91
Indinavir	1.10
Nelfinavir	1.12
Saquinavir	0.96
Stavudine	1.09
Tenofovir	0.97
Zalcitabine	0.99

Implications of these studies. While the D:A:D study has the benefit of size and prestige behind it, the French study used patient-level data. Thus, doctors asked which they believed drew the line somewhere in between, saying Ziagen is probably a little worse but still a viable option for individual patients. So far, most agreed that the D:A:D findings carried the most weight, but several said the French study continues to keep abacavir alive despite the D:A:D results.

In another talk at CROI, Dr. Peter Reiss of Academic Medical Center in Amsterdam reviewed the CV safety of abacavir.

➢ **The problem.** The relative risk of an MI with recent (last ≤6 months) use of abacavir in the D:A:D trial was 1.94 (p=0.0001), the relative risk with past use ~1.25, and the cumulative relative risk ~1, suggesting an "on=off phenomenon." Some experts have suggested that this risk is due to "channeling bias," with persons perceived to be at risk of CV disease preferentially prescribed abacavir, but Dr. Reiss said that was unlikely because the risk of abacavir:

- Was not reduced by adjusting for known risk factors, including those possibly affected by ART.
- Was no longer present after the drug was discontinued.
- Is specific for MI and other outcomes related to coronary artery disease but not for stroke, which might be expected to be affected by the same bias.
- The same effect was not seen with tenofovir which also could be expected to be preferentially prescribed to CV disease patients.

In the SMART trial, abacavir, adjusted for CV risk factors, was associated with a relative risk (RR) of developing: any CV disease = 1.9, minor CV disease = 2.7, MI = 4.3, and major CV disease = 1.89. In the STEAL study presented at CROI, serious non-AIDS events and CV disease were both higher with abacavir than tenofovir [4.4% vs. 1.2% (p=0.18), and 2.2% vs. 0.3% (p=0.046), respectively]. In the French ANRS study, patients exposed to abacavir <1 year and with a viral load ≤50 copies/mL had an overall risk of 6.12 of an MI vs. a risk of 0.95 with a viral load >50 (p=0.045).

➢ **Speculation on pathogenesis.** Possible mechanisms include: atheroma formation and growth; plaque instability and rupture; and thrombosis. Dr. Reiss said consistently increased platelet aggregation has been observed in abacavir patients, and the clinical data suggest a (sub)acute, reversible, rather than gradual, progressive pathogenic mechanism. He said animal and biomarker studies may shed more light on this issue.

➢ **Clinical ramifications.** Dr. Reiss said the abacavir risk seems more pronounced in patients with higher underlying CV risk, so a "common sense approach" may be in:

- **Patients at moderate-to-high CV risk:** Switch to another drug if one is available and if not, continue abacavir. In either case, manage the modifiable underlying CV risk factors.
- **Patients at low CV risk:** Continue abacavir if there is no alternative agent. If there is an alternative agent, then doctors and patients can choose either to continue or to switch.

Physician comments continue to suggest they are concerned with the findings but not abandoning abacavir:

- "I still think the data (on the CV risk of abacavir) are not conclusive. You can't ignore the drug or the signals. If all things are equal, in high-risk patients, I'd factor this in as another risk factor. In known CV risk patients, you try to construct a regimen without it if possible. Patients without antiretroviral therapy will get more MIs than people on antiretroviral therapy, so the risk of no medication is worse than abacavir, and the abacavir risk is very low…I don't take patients off it if they are stable and not a dramatic CV risk."
- "It is still a struggle to understand this issue. There appears to be a signal. The magnitude of the increase is in patients with other underlying risk factors. It has to be taken in context. I'm still struggling with how to respond to it in practice. You probably should think about switching patients with a lot of other risk factors – patients at high risk – but leave patients on it if they are doing well and at low risk."
- "We don't use abacavir a lot because of our own access issues, not because of the MI risk. At the end of the day, in patients with significant cardiovascular risk, there is no option but to act on the data…And we still don't have long-term data to tell us the real CV risk with tenofovir. All drugs in that class cause problems. I'm not giving up on abacavir, but it was heavily prescribed because it seemed safer, and now the dark side has appeared."
- "My job is to treat HIV, and I'll worry about other issues (like CV risk) later. I'm not sure tenofovir is better; it is associated with osteoporosis and renal issues."

NEUROCOGNITIVE IMPAIRMENT (NCI) IN HIV

Neurocognitive problems were an early and serious problem in HIV, but the general thinking has been that this is much less of a problem in the current era of antiretroviral therapy. However, data presented at CROI suggested that neurocognition remains a problem, and that the choice of ART should be based, at least in part, on the drug's ability to penetrate the blood brain barrier.

Dr. Igor Grant of the University of California, San Diego, presented new findings from the CHARTER trial, a 1,555-patient cross-sectional study at 6 sites that looked at neurocognition in HIV patients. The study found that, using standard assays, the viral load in cerebrospinal fluid (CSF) was higher than in plasma in 4.7% of patients (by 0.53 $\log_{10}$ copies/mL), and 0.9% had detectable levels in the CSF but undetectable levels in plasma. However, using a more sensitive assay, researchers discovered that among the patients for whom they had CSF samples:

- 41% of patients with viral load <50 had detectable virus in the CSF.
- Detectable virus in the CSF was associated with a worse cognitive performance score (p=0.03).
- 26% of patients with detectable virus in the CSF had undetectable levels in their blood, and this was associated with worse cognitive performance.
- 57% of patients had evidence of peripheral neuropathy, and the risk increased with age, antiretroviral therapy, and the CD4 nadir.
- One-third of patients studied had MRI evidence of white matter abnormality. Worse neurocognitive performance is associated with grey and white matter atrophy and greater abnormal white matter.
- HIV-associated neurocognitive disorders (HAND) was less likely in patients treated with combination ART (cART) who achieved undetectable plasma viral load and had no history of severe immunosuppression.
- cART with higher CSF penetration reduced CSF viral load better than therapies that did not penetrate the CSF.

Dr. Grant concluded, "From 40%-50% of patients receiving very good treatment still have neurocognitive complications, so there is a divergence between the process in the brain and what is going on in the rest of the body."

How serious are these neurocognitive deficits? Dr. Grant said, "Probably 25% have test impairments that the persons themselves may not be aware of or the family might not pick up…The rest have enough impairment that it affects day-to-day functioning in some manner – the ability to manage complex medication regimens or perform the same level of

work. Roughly speaking, maybe half or so are asymptomatically impaired. The prevalence of very severe impairment is very low, about 2%, and this tended to be much higher in the pre-treatment era."

What predictors are there of which HIV patients are at risk for neurocognitive complications? Dr. Grant said, "One important predictor was nadir CD4 count – the lowest level of CD4 a person has experienced. That was associated with a likelihood of cognitive impairment. Put another way, people who never had severe immunosuppression and whose treatment was effective in eliminating the virus from plasma were the least likely to have brain impairment. The implications of this are that there may be events that perhaps occur early in the course of infection, such as severe immunosuppression, that may…leave a legacy or effect on the brain. If that is true, that raises the question of whether treatment guidelines might need to be adjusted to begin earlier, more aggressive treatment."

Is high viral load more of a factor in NCI than low CD4 count? Dr. Grant said, "This is a complicated issue. We looked at both plasma viral load and CSF viral load, and it looks to be the case that if there is persistent viral replication in the CSF, that is more likely to be associated with the presence of NCIs. What the (CHARTER) trial found in particular is that there is a group of patients in whom plasma viral load is undetectable, but if you use a very sensitive assay, you can still detect virus in the CSF, and in those patients neurocognitive impairment was somewhat more likely."

Does it make a difference which antiretroviral therapy a patient takes? Yes. Not all antiretrovirals are created alike in terms of their ability to penetrate the CSF. Dr. Grant said, "As a general rule, NNRTIs fairly well penetrate into the central nervous system, whereas most protease inhibitors are poor penetrators. Zidovudine (GlaxoSmithKline's Retrovir, AZT) is somewhere in between…People on better penetrating drugs are more likely to have undetectable viral load in the CSF, and they are also somewhat less likely to have cognitive impairment."

The very last talk at CROI was devoted to a further look at this issue. Dr. Scott Letendre, also of the University of California, San Diego, said three factors determine the CNS penetration of a drug: fat solubility, molecular size, and physical chemical characteristics. He pointed out that other studies have found:

- 39% of patients had at least mild cognitive impairment.
- 26% had mild-to-moderate impairment.
- 22% had sustained impairment.

Dr. Letendre said antiretroviral therapy does not prevent HAND. In CHARTER, on which he worked with Dr. Grant:

- 10 patients on ART presented with neurological symptoms, and all had blood viral loads <500 c/mL.
- All had viral loads in the CSF ≥1 $\log_{10}$ c/mL higher than in blood.
- When the ART was modified based on genotype and cognitive performance score, seven had reduced viral load (<200), and all the patients improved clinically.

Dr. Letendre suggested how doctors might screen and diagnose neurocognitive problems in their patients, using patient questionnaires, brief screening tests, blood biomarkers (such as C-reactive protein), and neuroimaging. Once a problem is diagnosed – or in patients anxious to avoid developing a problem, it comes down to a choice of which antiretroviral agent to use. Dr. Letendre offered some advice and an overview of the penetration capability of a number of agents:

- Patients with HAND who ***are not*** on ART – consider initiating therapy with a "more neuro-effective regimen." He said this is the "most strongly supported scenario, consistent with findings from observational studies, and a randomized trial is in progress" to test this approach. He added, "We know there is a risk with switching, so this is not something that should be done lightly but which can be considered." Also consider adjunctive therapies like Forest Laboratories' Namenda (memantine).
- Patients with HAND who ***are*** on ART – consider switching therapy from a less neuro-effective drug to a more neuro-effective regimen. He said this approach is also "supported by existing observational data," but he advised doctors to consider risk of failure and toxicity when changing therapy. No clinical trial of this approach is yet underway. Consider adjunctive therapies like Namenda.
- In all patients, regardless of cognitive status – consider initiating ART with a more neuro-effective regimen. He

Antiretroviral Drug Penetration of the CNS

Drug class	High penetration	Intermediate penetration	Low penetration
NRTIs	Ziagen (abacavir) Retrovir (zidovudine)	Emtriva (emtricitabine, FTC) Epivir (lamivudine) Zerit (stavudine)	Viread (tenofovir) Hivid (zalcitabine) Videx (didanosine, DDI)
NNRTIs	Rescriptor (delavirdine) Viramune (nevirapine) **IC_{50} 100-fold**	Sustiva (efavirenz) **IC_{50} 20-fold**	---
Protease inhibitors	Agenerase-r (amprenavir) Crixivan-r (indinavir) Kaletra (lopinavir-r)	Agenerase (amprenavir) Crixivan (indinavir) Reyataz (atazanavir) Reyataz-r (atazanavir)	Viracept (nelfinavir) Norvir (ritonavir) Invirase (saquinavir) Invirase-r (saquinavir) Aptivus-r (tipranavir)
Fusion/entry inhibitors	---	---	Fuzeon (enfuvirtide)
Integrase inhibitors	---	---	Isentress (raltegravir) **IC_{50} 3-fold**
CCR5	Selzentry (miraviroc) **IC_{50} 100-fold**	---	---

* r = ritonavir

said this approach is "indirectly supported" by existing observational data, but no clinical trial is yet being performed, adding, "Since some patients are not at risk for HAND, treating all patients with CNS-optimized antiretroviral therapy may not be necessary."

While Merck said the blood brain barrier penetration of raltegravir is not known, Dr. Letendre said he was able to estimate it in the low category. But he pointed out that it may be increased if taken with food, "Merck looked at taking raltegravir with food and the plasma concentration and found no relationship, but the therapeutic index with CSF is more sensitive. So, it ***could*** be that if you take raltegravir with food, it ***might*** get it in."

Should all patients be started on more neuro-effective regimens? Dr. Letendre said, "We know there are other risk factors – bone, renal, etc…So, this isn't a decision that can be made in a vacuum. The answer is no. You have to consider potency based on resistance testing, past toxicities, etc." Dr. Judith Currier of the University of California, San Francisco, said, "The significance of these findings are that doctors need to be mindful and pay attention to cognitive function. Some neurologists in this area do look at this. We don't have effective studies that show that if you change, the patient improves. One of the things I might do is start patients on treatment earlier, and we are already at 350…My principal NNRTI is Atripla, which is attractive for a lot of reasons. If this is an added advantage, I don't know yet."

Two trials are underway that should shed more light on this issue:

- **CIT2, a cognitive intervention trial.** This NIMH-funded, randomized trial is enrolling patients at 3 sites (Johns Hopkins, Washington University in St. Louis, and the University of California, Davis), looking at the effectiveness of CNS-optimized antiretroviral therapy.
- **ACTG-5241, an options study.** This randomized trial, sponsored by NIAID, is looking at the effectiveness of NRTI-sparing antiretroviral therapy in the CNS. It also is enrolling patients.

ANTIRETROVIRALS

Several new HIV drugs are in development – including Ardea Biosciences' RDEA-806, RDEA-427, and Gilead's GS-9350 and elvitegravir, but there was more attention at CROI on issues surrounding already approved drugs from the cardiac safety of Ziagen to a failed switching study for Isentress.

ARDEA BIOSCIENCES' RDEA-806 and RDEA-427

Barry Quart, president of Ardea, said RDEA-806, the company's lead agent, is in Phase II trials. RDEA-427 (an NNRTI) was described as a next generation agent (or backup agent) to RDEA-806. According to Quart, the main advantage of RDEA-427 is its different scaffolding, making it structurally different from RDEA-806 and giving it a very long half-life. Quart said both agents have excellent antiviral activity.

A poster on RDEA-427 was presented at CROI on an *in vitro* resistance study and PK properties of RDEA-427. Researchers said the data showed RDEA-427:

- Is active against NNRTI-resistant mutation viruses, including prevalence transmitted viruses and etravirine (Johnson & Johnson/Tibotec's Intelence) resistance associated mutations (RAMs).
- Has a lower potential for CYP3A4 induction than etravirine or TMC-278 (J&J, rilpivirine).
- Has better metabolic stability and lower covalent binding than TMC-278.
- Has a mean half-life of 41 hours, indicating it could be a once-daily drug.
- Had no lab adverse events, and no clinically relevant abnormalities in laboratory tests were observed during a microdose study.

How does Ardea plan to develop these drugs? Quart said, "For these two drugs, we are moving forward on our own, but we are interested in partnering. There are 10 companies in HIV, and half of them are very active, including Bristol-Myers Squibb, Merck, and GlaxoSmithKline, which just in-licensed another NNRTI."

With a number of NNRTI's already on the market, where do Ardea's drugs fit? Quart said:

1. **In naïve patients as an alternative to Bristol-Myers Squibb's Sustiva (efavirenz)**, an NNRTI. Quart said, "We already demonstrated that RDEA-806 is not teratogenic, and Sustiva is."
2. **In patients of African descent.** Ardea's drugs do not metabolize CYP450 2B6 which Sustiva does. About 20% of people of African descent reportedly are slow metabolizers of 2B6, so they get very sick from Sustiva.
3. **To avoid drug-drug interactions.** Ardea's drugs do not induce or inhibit liver metabolism, so they are likely to have fewer drug-drug interactions. For example, they are not expected to interact with methadone as Sustiva does.

COMBINATION ANTIRETROVIRAL THERAPY

Both Gilead's Truvada (tenofovir + emtricitabine) and Atripla (efavirenz + emtricitabine + tenofovir) are very popular as initiation combination therapy. Atripla appears to be continuing to gain market share, but Truvada is still commonly used. Comments included:

- "Truvada is most commonly used because it is used in people on a protease inhibitor as well, but Atripla as initial therapy is very popular."

- "I use a lot of Atripla because it is easy and patients want it – much to the distress of the protease inhibitor sales reps, but my Atripla use will probably hold pretty steady now."
- "First-line I use Atripla or 2 nukes and an integrase inhibitor or a boosted protease inhibitor…Atripla never lost a trial. You see viral failures, but no excess…I use a lot of Atripla, and the rest of the patients get Truvada plus something else. My use of Atripla will probably hold steady over the next year…Combivir (GlaxoSmithKline, lamivudine + zidovudine) use is going away, and Epzicom (GlaxoSmithKline, abacavir + lamivudine) use is increasing. The market has pretty much shaken out."

HEAT trial. This head-to-head study of Epzicom vs. Truvada had been previously presented, but a poster at CROI found that both drugs similarly decreased inflammatory markers associated with CV risk in antiretroviral-naïve patients. Few CV events occurred in the trial, and the event rate was similar between the two drugs. Researchers concluded that biomarker changes do not support the hypothesis of an abacavir-induced inflammatory response leading to increased CV risk.

STEAL trial. A head-to-head comparison of Truvada and Epzicom found the two drugs had similar virological efficacy, but Epzicom was associated with more serious non-AIDS events, particularly CV disease and lipids, while Truvada caused more bone mineral density (BMD) loss. STEAL was a 360-patient, 96-week non-inferiority study sponsored by the Australian government and designed to see which once-daily fixed dose combination had the best efficacy and safety.

STEAL Trial Results: Truvada vs. Epzicom at 96 Weeks

Measurement	Truvada n=179	Epzicom n=178	p-value
Primary endpoint: Virological failure (repeat viral load >400) *	3.9%	5.6%	Nss, 0.62
Secondary endpoints (rate per 100 patient-years)			
Secondary endpoint #1: Serious non-AIDS events	1.2	4.4	0.018
Death **	1	3	---
CV disease	0.3	2.2	0.046
Secondary endpoint #2: Lipids (new cholesterol >6.5 or increase >2 mmol/L; new HDL <0.9 or decrease >0.5 mmol/L; or new therapy)	6.1	13.9	0.003
Secondary endpoint #3: Bone	8.5	4.4	0.032

* by an intent-to-treat, missing=failure analysis ** All were due to cancer

INTEGRASE INHIBITORS

Doctors are very enthusiastic about integrase inhibitors. Currently, Merck's Isentress (raltegravir) is the only FDA-approved integrase inhibitor, but other integrase inhibitors are in development, including Gilead's elvitegravir and GlaxoSmithKline's GSK-1349572. And a little reality appears to be settling in; doctors have pulled back just slightly in their enthusiasm and are looking at new indications a little more cautiously.

Comments about integrase inhibitors included:

- "Isentress is a very important drug. That drug will save a lot of lives. Is it a class thing or just a particularly good drug? I think it is a particularly good drug in the class… But, based on inertia, I don't think it will become a first-line drug. Truvada or Atripla are pretty well established as the first-line therapy. QD therapy is attractive first-line (Isentress is BID)." This doctor also suggested Isentress is mechanistically different from other drugs in the integrase class.
- "Protease inhibitors + efavirenz (Bristol-Myers Squibb's Sustiva) have a lot more potential to lower virus quickly, and raltegravir doesn't have nearly the potential. So, though integrase inhibitors are very good for salvage, there is concern about their use first-line. Initially, people thought an integrase inhibitor would be the anchor (first-line) – such as raltegravir + Truvada – but Dr. Siliciano showed good reasons for using a boosted protease inhibitor instead…The drugs that do best in Dr. Siliciano's assays have performed best in clinical trials, but that study is not finished for raltegravir. Don't get too excited before we see that data."
- "Elvitegravir is interesting because Gilead is working on it as part of a quad pill. That's interesting. Elvitegravir got a bad rap from the first study because it didn't measure up to raltegravir, but the raltegravir study was against darunavir (J&J's Prezista) which was an easier comparison."

MERCK's Isentress (raltegravir). The good news for Isentress was that doctors continue to be impressed with its efficacy. The bad news was that the results of a two-part study suggested patients who are stable on Abbott's Kaletra (lopinavir + ritonavir) probably should ***not*** be switched to Isentress.

Dr. Joseph Eron of the University of North Carolina presented the results of SWITCHMRK – which consisted of two identical, multicenter, double-blind, active-control studies (Protocols 032 and 033) in patients who were well controlled and stable on Kaletra in combination with at least 2 NRTIs (but no other active protease inhibitor). There were no serious drug-related adverse events or deaths in the two studies.

The SWITCHMRK trials had two primary endpoints:

1. **Lipid change at Week 12 – met.** Total cholesterol and triglycerides were significantly reduced with Isentress, but there was no impact on LDL or HDL.
2. **Viral load <50 copies at Week 24 – not met.** Not only did Isentress fail to meet the criteria for non-inferiority, but it was numerically inferior to Kaletra. A meta-analysis of the two trials together found efficacy 89.6% with Isentress and 94.4% with Kaletra.

Investigators suggested that patient selection may explain why Isentress patients did not do as well as Kaletra in terms of viral load suppression. The patient population was very heterogeneous with regard to prior antiretroviral therapy. A post hoc analysis found that most failures in Protocol 033 occurred early. In Protocol 032, 95% of the patients suppressed at Week 12 remained suppressed at Week 24. Overall, 84% of the Isentress patients with confirmed viral failure (>50 copies) reported that their regimen at study entry was not their first ART regimen, and 66% reported a history of viral failure on prior regimens. Merck senior director for clinical research, Dr. Bach-Yen Nguyen, added, "The reason why you did not see the 87% (viral suppression) that you saw with Kaletra in 032 and 93% in 033 is potentially because the patients don't have an optimal background regimen…Background therapy is important…The maximum efficacy (with Isentress) is when it is used with an active regimen, and SWITCHMRK enforced that notion…The reason we didn't see a higher viral effect was that the patients already had compromised background therapy."

Asked what recommendations he would have for clinicians based on these trials, Dr. Eron said, "I think that one needs to be extremely cautious about switching medications and regimens making a drug substitution to raltegravir…We ought to be cautious…If you don't know the effectiveness of the background therapy, you need to be quite careful." Dr. Nguyen added, "If patients are intolerant of current Kaletra therapy because of severe lipid problems or lipodystrophy, we don't have the data to say what to do. We are limited to the conclusions from Protocol 032 and 033 in Kaletra-tolerant patients."

Dr. Nguyen said that, based on the virological results, Merck has decided to terminate the study and, at this point, is not planning to do another switching study. However, some investigators are hoping that the trial will be re-started.

Enrollment in a trial of Isentress in pediatrics has been put on hiatus while the dose is changed, a raltegravir researcher said. Enrollment is expected to re-open in the next few weeks.

Merck has already filed a supplemental NDA (sNDA) with the FDA seeking approval of Isentress as a first-line therapy in HIV, and experts were divided on whether the SWITCHMRK study would have any influence on the FDA's decision. Dr. Nguyen said, "The data from this (SWITCHMRK) have absolutely no impact on efficacy and safety data we have in treatment-naïve patients. In treatment-naïve patients, with Truvada + raltegravir, we demonstrated very rapid viral suppression that is non-inferior to Truvada at Week 48 and is also supported by 96-week data from a Phase II trial which showed the same thing. We have two Phase III studies that clearly demonstrate the benefit of treatment (in naïve patients)."

Another issue that could impact the FDA's decision on approval of Isentress for first-line therapy is its penetration into the central nervous system. Merck officials said there are no clinical data on Isentress crossing the blood brain barrier in humans, but it is a water-soluble molecule, with a molecular weight of 482.51. However, an outside expert said Isentress has a very low ability to cross the blood brain barrier.

Other comments about Isentress included:

- "The toxicity (with Isentress) is lovely…but whether it can be used first-line remains to be seen."
- "BID dosing is not a deterrent in pediatrics or adults. The bad aspect of QD dosing is that non-compliance is worse in patients on that regimen."
- "I have no enthusiasm for switching patients doing well on other drugs to raltegravir."
- "I was switching stable patients (from other drugs to raltegravir). There are some switching studies where it worked. The issue is choosing the right patients. The design of SWITCHMRK was terrible. They put some patients in that trial who should never have been in the trial, and they had some wrong investigators, too…The first-line study worked pretty well…I think you simply must select your patients and know what you are doing…Use will increase because it is a strikingly effective drug, just not perfect."

Results of SWITCHMRK

Measurement	Protocol 032		Protocol 033	
	Isentress n=174	Kaletra n=174	Isentress n=176	Kaletra n=178
Discontinuations	14.4%	9.8%	5.7%	3.4%
Primary endpoint #1: Viral load <50 copies at Week 24	81%	87%	88%	94%
Patients with confirmed virologic failure	13 patients	10 patients	19 patients	7 patients
Primary endpoint #2: **Mean change in lipids at Week 12**				
Total cholesterol	-13% (p<0.001)	+1%	-12% (p<0.001)	+1%
Triglycerides	-41% (p<0.001)	+4%	-43% (p<0.001)	+8%
LDL	-2% (Nss, p=0.704)	+2%	+4% (Nss, p=0.269)	+1%
HDL	-1% (Nss)	+1%	-1% (Nss)	-3%

- "The differences are very small, but they are differences. The major message is: make sure the patients' other two drugs are effective (in a 3-drug regimen). You have to know the efficacy of all the drugs a patient is taking. Raltegravir is a good drug, no question; it has less barrier to mutation. It could be first-line if you know the total package."
- "SWITCHMRK definitely will cause people to pause and put off switching."
- "This was a poorly designed study, and that is the problem. The outcome was predictable. We switch patients (to raltegravir), but we look at what the patient is left with, and we ***never*** use raltegravir monotherapy."
- "I'm continuing to use raltegravir but only in combination."
- "It will very much chill enthusiasm for raltegravir if it doesn't cross the blood brain barrier and would prevent it from becoming a first-line drug."

MISCELLANEOUS

NRTI-sparing approaches. The idea of drug holidays was proven to be a bad idea in HIV, but NRTI-sparing approaches are getting attention. An expert explained, "People are interested because of the toxicity of the nucleosides – AZT and DDI. Truvada is very well tolerated, but Viread does cause renal damage, and in people without normal kidneys, the damage can be quite serious…When Truvada came along, it was a huge advance, but it was tested in normal kidney patients. When you use it in patients with underlying kidney problems, it is a different story. There, we do see problems with kidney toxicity. So there is an effort by physicians to find an alternative."

ROCHE/TRIMERIS's Fuzeon (enfuvirtide). Sources said use of Fuzeon is relatively flat at a very low level. One quipped, "If we do a lot more stupid switches to raltegravir, we may need it again because people will blow through their options. It is very, very effective but inconvenient."

VIROCHEM's VHC-286, a CCR5 antagonist. In a poster, ViroChem researchers provided some kinetic and *in vitro* data on this investigational agent. They showed that it has a slower off-rate and a prolonged CCR5 receptor occupancy vs. Pfizer's Selzentry (miraviroc). They suggested that VHC-286 might have an advantage over miraviroc by achieving a higher occupancy rate on the cell surface CCR5 receptor – that is, it might be a more effective blocker.

IMMUNE BOOSTING DRUGS:
NOVARTIS's Proleukin (IL-2) – not beneficial in HIV

It cost almost $100 million to find out, but researchers now know recombinant interleukin-2 (IL-2) is not an effective treatment in HIV. Two trials presented at CROI found absolutely no clinical benefit to adding subcutaneous injections of IL-2 to antiretroviral therapy, and the therapy increased adverse events. But the findings could have broader implications for immune-based therapy in other diseases.

Researchers agreed that the results of the ESPRIT and SILCAAT trials spell the death knell for IL-2 in HIV. ESPRIT principal investigator Dr. Marcelo Losso of Hospital José María Ramos Mejía in Buenos Aires, Argentina, said, "I think this trial provides a definitive answer about the clinical value of the drug in HIV." SILCAAT principal investigator Dr. Yves Levy of Hospital Henri Mondor in Créteil, France, agreed, "I don't see any possible development of IL-2 based on these data." Dr. Richard Koup of NIH added, "The idea of using subcutaneous IL-2 injections to boost CD4+ T-cell counts in HIV is probably dead."

It was hoped that IL-2, by boosting the immune system, specifically CD4+ counts, patients on antiretroviral therapy would have a lower risk of opportunistic disease or death. IL-2 injections did raise CD4 levels. But that didn't translate to any clinical benefit. After a median follow-up of seven years, both ESPRIT and SILCAAT found no difference in the primary endpoint, death or opportunistic disease, with or without IL-2.

The results didn't surprise clinicians at the conference, and they said the data are unlikely to have a major impact on clinical practice. IL-2 is not widely used due to cost and side effects. Dr. Steven Fine of the University of Rochester Medical Center, said, "In the past, we used to use IL-2 to raise CD4 levels in patients who didn't respond to antiretroviral therapy, but the side effects are difficult to manage. Now, there are exceedingly few patients – with the improved

Efficacy of IL-2 in HIV

Measurement	IL-2	Control	Hazard ratio	p-value
ESPRIT Trial *(rate per 100 person-years)*				
Primary endpoint: Opportunistic disease/death	1.13	1.21	0.93	Nss, 0.52
All-cause death	0.75	0.83	0.91	Nss, 0.50
Serious non-AIDS events	1.01	0.99	1.01	Nss, 0.91
Grade 4 clinical events	3.82	3.07	1.24	0.0002
CD4 cell count change	153/mm^3 higher with IL-2		---	---
SILCAAT Trial *(rate per 100 person-years)*				
Primary endpoint: Opportunistic disease/death	1.92	2.12	0.91	Nss, 0.70
All-cause death	1.38	1.32	1.06	Nss, 0.73
Grade 4 clinical events	3.97	3.61	1.10	Nss, 0.34
Any opportunistic disease	0.85	1.17	0.73	Nss, 0.10
CD4 cell count change	57/mm^3 higher with IL-2		---	---

therapies we have – that don't have a CD4 response with antiretroviral therapy. I haven't had occasion to use IL-2 in many years." A Pennsylvania doctor added, "IL-2 has been the great hope, but no one uses it outside of a trial. It is not something we are losing from the armamentarium. We are losing it from hope."

ESPRIT was a 4,011-patient trial conducted in the U.S. and 24 other countries. The Kaplan-Meier curves for an event were identical for the first four years, and then the curves separated slightly, favoring no IL-2. Grade 4 adverse events occurred in 466 IL-2 patients vs. 383 control patients (p=0.003, hazard ratio 1.23 favoring control).

Dr. Losso said ESPRIT, which added IL-2 in patients with already high CD4 levels (>300), "provides a clear answer on the lack of clinical value of providing the drug." The trial also found a significant increase in Grade 4 adverse events, including fever, site infections, and deep vein thrombosis (DVT).

Likewise, Dr. Levy said SILCAAT, which added IL-2 in patients without a CD4 response (<299) from antiretroviral therapy, makes it "clear now that there is no benefit to receiving this in combination with antiretroviral therapy." There was not an increase in Grade 4 adverse events in SILCAAT, only what Dr. Levy called "expected IL-2 side effects."

SILCAAT was a randomized, international trial in 1,695 patients. It was stopped early because of the ESPRIT results. The Kaplan-Meier curves for an event diverged at just under three years, and slightly, but non-significantly, favored IL-2 through the remainder of the study. Grade 4 adverse events were significantly more frequent with IL-2 in the first year of the trial, but not significantly different after that. However, Grade 4 gastrointestinal and psychiatric events were significantly higher with IL-2 throughout the trial (p=0.01 and 0.03, respectively).

The problem in these trials was not the choice of the wrong cytokine to boost the immune system, Dr. Levy said, "I would say we should come back to basic science." Phase I trials have begun with another cytokine, IL-7, and he does not think that study should be abandoned because of the failure of IL-2. Dr. Losso added, "One of the most important findings of this trial is that when you use a surrogate marker like CD4, you could have some surprises regarding the effect on the clinical outcomes, and that could be applied to IL-7 eventually."

Yet, these trials may have a broader impact on drug development. Dr. James Neaton, a professor of biostatistics at the University of Minnesota, said Chiron, which initially funded these studies abandoned its plan to get an HIV indication for Proleukin because "the FDA would not give accelerated approval based on CD4 count." Dr. Neaton, who was the principal investigator of INSIGHT, which oversaw the ESPRIT trial, and the principal investigator of the grant for the SILCAAT trial, said that these trials have implications for how immune-based therapies are developed for other diseases. He said a meeting will be convened soon of immunologists inside and outside the HIV field "to discuss what we know and don't know about the immune system."

PHARMACOKINETIC (PK) ENHANCERS: GILEAD SCIENCE'S GS-9350 and SEQUOIA PHARMACEUTICALS' SPI-452

Replacements are in the wings for Abbott's Norvir (ritonavir), which is used to "boost" systemic exposure of protease inhibitors in HIV patients, and doctors at the 16th Conference of Retroviruses and Opportunistic infections are excited about them. Data presented at the conference suggested that both Gilead's GS-9350 and Sequoia's SPI-452 are equally or more effective than ritonavir but with a more favorable profile.

These new pharmacokinetic enhancers (PKEs) have no antiviral activity. Both work using the same mechanism of action as ritonavir, irreversibly and potently blocking cytochrome P450 3A (CYP3A) activity, which boosts the efficacy of other HIV drugs, particularly protease inhibitors.

However, both GS-9350 and SPI-452 appear to have several advantages over ritonavir, including:

- Fewer metabolic side effects than ritonavir (fewer elevations of triglycerides or cholesterol).
- Fewer gastrointestinal side effects.
- More specific CYPA inhibition. GS-9350 has less effect on CYP3A 2D6, for instance.

GS-9350 also reportedly is tasteless while one of the barriers to patient adherence to ritonavir is its unpleasant taste, and it doesn't cause the induction which occurs with ritonavir. SPI-452 may be able to be formulated as a once-a-day drug in the future.

Even if these drugs didn't have advantages over ritonavir, doctors would still be interested in them. Dr. Mellors described ritonavir as a "bottleneck in effort to co-formulate medications. Our strategy has been dependent on one molecule, which is the property of Abbott. There has been a hue and cry and various protests about the availability of only one boosting agent, and there has been concern at the regulatory level and among clinicians on the effects of a boosting agent such as ritonavir used without a protease inhibitor, such as with an integrase inhibitor like elvitegravir (Gilead). So we applaud the efforts of Gilead and Sequoia."

Dr. Coffin of Tufts said the new PK boosters are important, in particular, because "people would like not to deal with Abbott if they didn't have to. There is a lot of bad blood there." He added, "Ritonavir is kind of a blunt instrument, and something more refined might be better."

GS-9350 is a soluble solid dosage formulation that Brian Kearney, PharmD, senior director of clinical research at Gilead, described as "smaller than Atripla (Gilead/Bristol-Myers Squibb, efavirenz + emtricitabine + tenofovir). Dr. Kearney also said GS-9350 is "amenable to co-formulation" with other antiviral drugs, including integrase inhibitors. So it could, potentially, be combined with other drugs. In fact, Gilead plans to begin two Phase II trials in naïve patients in the second quarter of 2009, one with GS-9350 as a stand-alone agent and one as part of a quad drug vs. Atripla. The quad drug would be a combination of GS-9350 plus three other Gilead drugs: elvitegravir (an integrase inhibitor which is not yet FDA approved), tenofovir (Viread), and emtricitabine (Emtriva).

At CROI, two studies of GS-9350 – a single-dose and an open-label, partially randomized, 14-day multiple-dose escalation study of the quad formulation in 44 patients – showed that GS-9350 had less effect on adipocytes and proteasome activity than ritonavir. The final dose chosen to go forward is 150 mg.

Dr. Kearney said GS-9350 has greater enzyme specificity than ritonavir and less induction of drug-metabolizing enzymes and transporters, including human pregnane X receptor (hPXR), which plays a key role in the regulation of both drug metabolism and efflux.

In terms of safety, in the first-in-man study GS-9350 had no changes or differences in serum lipids and no Grade 4 lab abnormalities, though there was one patient with a Grade 3 "discoordination" at 100 mg. Dr. Kearney explained that this was a juggler who felt her juggling ability was impaired by the drug.

In the quad study, Dr. Kearney said all patients tolerated the therapy well, but there were two Grade 3 adverse events; one patient with acute appendicitis and one patient with drug-related alanine aminotransferase (ALT) elevation. The liver enzyme elevation was transient and began to decrease on the drug, but the patient was still withdrawn from the trial, and the ALT level returned to normal. No other drug-related adverse events were reported. Doctors did not appear too concerned with the ALT case, but they were curious about the discoordination patient.

GS-9350 vs. Ritonavir

Measurement	GS-9350	Ritonavir
K_{inact} (min -1)	0.44	0.23
K_I (µM)	0.94	0.26
% inhibition of glucose uptake at 10 µM	9.5	55

GS-9350 vs. Elvitegravir + Ritonavir

Measurement	GS-9350 150 mg	Elvitegravir + ritonavir
AUC	27000	22500
C_{max}	2660	2500

In a first-in-man, Phase I, dose-escalation study, SPI-452 also showed very good PK enhancement compared to ritonavir and significantly lower triglycerides and LDL cholesterol. SPI-452 had more side effects than GS-9350 – 19% of patients had one or more adverse events (4 headaches, 4 sore throats). Then, a Phase II study, comparing SPI-452 to saquinavir (Roche's Fortovase), 45 of the 67 patients had one or more adverse events. These were usually mild, including 17 with headache, 11 nausea/emesis, and 7 diarrhea. There was no QT prolongation and no change in serum lipids.

However, Robert Guttendorf, PhD, vice president of pharmacology at Sequoia, insisted that GI side effects were lower with SPI-452 than with ritonavir. He said solubility is fairly low, but the company was able to formulate its drug as a solid oral dispersion formulation in a way that has good bioavailability. Dr. Guttendorf said there will be an induction effect at the front-end with SPI-452, just as with ritonavir.

Asked why SPI-452 was not directly compared to ritonavir, Dr. Guttendorf said that will be done with other trials the company is planning. He said, "We believe SPI-452 has great potential, potentially as a stand-alone agent or a fixed dose application. It also has application for other types of classes of antiretrovirals, and in hepatitis C it would be a good adjunct to some agents. And there is a possibility for SPI-452 or our PKE platform to be applied outside the HIV area."

Sequoia is a small company, but it currently is developing SPI-452 on its own, though Dr. Guttendorf said Sequoia is in discussions with other pharmaceutical companies about a combination product, "We are in discussion with a number of potential large pharma companies on a fixed dose. We intend to bring this forward as a stand-alone tablet as well as a combination product."

Asked about plans to combine SPI-452 with a protease inhibitor – boceprevir (Schering-Plough) – to treat hepatitis C, Dr. Guttendorf said, "At this point, we have proof of concept *in vitro* that we can enhance boceprevir, and we are doing animal studies now. Because it is a new molecular entity (NME), we would need a collaboration and probably a new investigational new drug application (IND) with Schering-Plough, but we do look at that as an opportunity... Beyond antiretrovirals, our PKE platform is fairly broad reaching. We have additional compounds in the pipeline that could come in as stand-alone or combinations for HIV, HCV, or elsewhere."

Kimberly Struble, PharmD, with the FDA's Division of Antiviral Drug Products, one of the session moderators, offered some guidance on the regulatory hurdles for GS-9350, SPI-452, or any other new PK enhancer. She said that the FDA would treat these agents like "any other products to treat HIV." She explained the FDA will want 24 weeks of safety and efficacy data on around 500 experienced patients and 48-week data in naïve patients.

Dr. Kearney of Gilead said they plan to study more than 500 patients for more than one year and a larger number of patients for a shorter period of time, "It is an NME, so we are expected to have the same data as a new antiretroviral…The number required for approval has to do with safety, and that can be generated from different studies and different combinations."

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