Trends-in-Medicine

July 2003
By Lynne Peterson

SUMMARY

Roche/Trimeris' Fuzeon (T-20) is a very niche product that will be used in <5% of patients, generally as 3rd or 4th line therapy. Demand, not supply, is the issue; there is no pent-up demand or waiting list due to the BID injections and cost. ♦ ~28% of patients are salvage, but most of these are due to non-compliance. ♦ Within a year, doctors expect to be using as much of Bristol-Myers Squibb protease inhibitor, Reyataz (atazanavir), as Abbott's Kaletra. Doctors are divided on whether to boost Reyataz with ritonavir in naïve patients, but they will boost it in experienced patients. ♦ Use of Gilead's Viread (tenofovir) continues to increase, and doctors are not concerned about reports of renal toxicity. Sales of Gilead's Emtriva (FTC) are likely to ramp slowly until a combination Viread/FTC pill is available, and then the combination will take significant market share from 3TC.

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INTERNATIONAL AIDS SOCIETY
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This was the second international IAS conference. This report selectively looks at some of the key agents that have recently been approved or are in development. In addition, 25 AIDS specialists were questioned at the meeting on various HIV-related topics.

The hot new drugs at the meeting appeared to be: Roche/Trimeris's Fuzeon (T-20) and Bristol-Myers Squibb's Reyataz (atazanavir). The outlook is for very restricted use of Fuzeon because of the BID injections as much as the $20,000 price tag, making demand more an issue than supply. Reyataz is starting to catch on, and doctors predicted it would capture significant market share from Abbott's Kaletra and Pfizer's Viracept (nelfinavir) within a year. Use of Gilead's Viread (tenofovir) is continuing to ramp up.

The most promising agents under development appeared to be: Johnson & Johnson/Tibotec's protease inhibitor TMC-114, Boehringer Ingelheim's protease inhibitor tripanavir, the CCR5s and the integrase inhibitors, but there was little data on any of these at the meeting.

Experts were pleased with the science presented at the meeting, but they agreed that a there is still lot of work to do in AIDS prevention and treatment. There are currently 22 drugs approved in the U.S. to treat HIV, with 19 unique agents and 3 combination products (See chart at end of this report). Dr. Anthony Fauci, Director of the National Institute Allergy and Infectious Disease emphasized that there has not yet been a documented spontaneous recovery from HIV, saying, "That is unprecedented. The science has to bridge that gap on why and how we cannot clear HIV from the body. So we need to do some of science if we are going to develop a vaccine."

Speakers generally agreed that perfect adherence (>90%) is required for best virologic outcome. The key factors interfering with HIV therapy adherence/compliance are:

1. Toxicity/side effects – GI, hepatotoxicity, dyslipidemia, drug-drug interactions, etc.
2. Frequency of dosing.

Dosing Regimen	Non-compliant patients
QD	40%
BID	63%
TID	66%
TID+	71%

3. Number of pills.

Combination	Number of pills	Frequency of dosing
D4T/3TC/indinavir	10	TID
ZDV/ETC/Efavirenz	5	BID
ZDV/3TC/EFV	3	BID
TDF/FTC or 3TC/EFV	3	QD

Missing a dose may be less important with once-daily drugs that have a long half-life. A speaker said, "With a BID or QD drug with a short half life, if a dose is missed, then you enter a zone of potential replication at about 24 hours…with a QD drug with a long half-life have a period of forgiveness if you miss a dose…You've been told it is worse to miss a dose on a QD regimen than on a BID regimen, but in reality the risks of a missed or delayed dose are dependent on the PK, not the dosing schedule."

How large is the salvage population?

Sources estimated that 300,000-400,000 Americans are being treated for HIV, with perhaps another 400,000-600,000 untreated. Sources estimated that, on average, 28% of the patients in their practices are salvage patients. The number of salvage patients is not going down, but we won't generate the same number of salvage patients as we did in the past, an expert said, explaining, "There will continue to be an increase in the number, but whether it is just a trickle or a huge increase is hard to project. I'm reasonably optimistic that, with the current first-line regimens, more and more patients will be fully suppressed and have long-term durable responses to first-line regimens, but, inevitably, there will be failures, and those today are usually due to toxicity or non-adherence."

Many of the salvage patients today have become resistant to all drug therapy because they got the wrong therapy in the beginning – even though they got what was thought to be the best therapy at the time. He commented, "Most of the patients today who need salvage therapy are patients who initially went on one or two drug regimens in the early 1990s. When protease inhibitors came about, though they were going on HAART, they were only adding one new drug, and they only had a temporarily response to the PI (protease inhibitor). They are the patients having the most trouble finding an effective regimen. Many were highly adherent but to regimens that were not fully suppressive."

Doctors said the majority (an average of 80%) of their salvage patients are salvage because of non-compliance with treatment regimens. They estimated that only 4%-5% of their patients would be salvage if they were compliant.

Prevalence of Drug Resistance in Europe

The CATCH study of 1400 patients in 14 European countries indicates that about 10% of people who are HIV+ have drug resistance, and the rate is similar to the U.S. Data from another 600 patients in the U.K. and France have not yet been analyzed. A researcher said, "Once these mutations have been transmitted, they seem to persist for a long time."

European CATCH Results of HIV Resistance in Europe

Category	% Resistant
Any naïve patient	9.6%
B subtype *	11.3%
Non-B subtype *	3.3%
NRTI	6.9%
NNRTI	2.6%
PI	2.2%
Multi-drug resistance (≥2 classes)	1.7%
Homosexuals	15.3%
Drug users	13.7%
Heterosexuals	11.6%

*Excluding Israel which has a large population of non-B

There are two subtypes of HIV, A and B. Most European HIV+ patients have the B subtype; in this study 69% of patients had the B subtype. A researcher said, "In Europe, we are seeing an increase of non-B subtypes coming mainly from Africa. In early U.S. and European experience, we started patients on suboptimal therapy, so the patients treated suboptimally created the resistance. If people were started on good HAART and were fully complaint, the resistance incidence would be <1%-2%." The president of IAS said, "I think we've taken absolutely the wrong approach to HIV...I think you need a national first line regimen and then backups…Make it as simple as possible, and for people with difficulties adhering, make sure there are support systems…In the Florida prison system, with supervised administration – Directly Observed Therapy (DOT) -- there was greater than 99% success. If you really accomplish close to that in the population, you won't have resistance…It won't happen here, at least not for the next 10-20 years. I'm dreaming. It should, but it won't happen. But it will happen in developing countries if they are smart."

Transmission of resistance also occurs sometimes in non-B subtype patients. A researcher said, "We think, based on CATCH, that baseline genotyping should be considered in newly diagnosed patients." The CATCH study also found that patients infected with the B subtype were resistant almost four times more often than non-B (11.3% vs. 3.3%)."

Studies printed last year in the ***Journal of the American Medical Association*** and the ***New England Journal of Medicine*** year found a 25% transmission rate in the U.S., but experts said populations measured in those studies were predominantly male homosexuals. A researcher said, "You can't compare the U.S. to Europe because in Europe health

insurance is different than in the U.S.; in Europe if you are infected with HIV, you get treated, which is not always the case in the U.S.…In Northern Europe, the HIV population is mostly homosexual men and only about 10% drug users; but in Southern Europe it is mostly drug users. In Italy more than 50% of people with HIV are drug users."

Intermittent Therapy

Most doctors strongly recommended against intermittent therapy in the U.S. They argued that HIV patients who are doing well should not "rock the boat" by discontinuing therapy, even for a short period of time. A speaker said, "In one study 3 of 18 patients had an increase in viremia with PI partial interruption, and 6 of 6 RTI patients had an increase in viremia with a partial interruption, but these are small numbers." Another expert said, "Partial interruption is interesting, but we lack data. In patients with undetectable viral load, there is a risk of suboptimal adherence and the risk of emergence of resistance virus. STIs (structured treatment interruptions) should be used with caution and essentially in the setting of clinical research only."

Yet, some doctors want to leave the door open for the use of intermittent therapy, particularly in developing countries, but they don't want to be accused having a double standard – one for the U.S. and another for less advantage countries. An expert said, "For most patients who have access to drugs, intermittent therapy is not a reasonable idea. We ought to wait until therapy is needed and simply treat patients. However, there may be circumstances where it is a reasonable option." Among the situations where intermittent therapy may be acceptable, he said, are:

- Patients who have had a substantial rise in CD4 but are experiencing toxicity, so we might interrupt therapy and wait for something better to come along and wait for CD4 to drift down.
- Treating until T cells rise to a certain level, then treating again, etc.
- To make more drug available in undeveloped countries.

Thus, some doctors, primarily non-U.S., physicians, suggested intermittent therapy (e.g., seven days on and seven days off) is a viable option, especially for developing countries where that approach could double the number of patients treated for the same cost, but also for patients who insist on a holiday from their drug regimen. Dr. Fauci said, "We are trying to make the therapeutic regimen user-friendly, particularly for use in developing nations. Drugs that require QD or at most BID or drugs that can be combined into one tablet, those are logistic advantages that will be very important in how easy it is to apply regimens to countries that don't have all the facilities that we have in developed nations such as France…We did studies in the U.S. and found that if you interrupt therapy long enough for the virus to rebound (a month or so) over multiple cycles, you get emergence of resistance, which is not a good thing…There are conflicting studies that 7-on/7-off doesn't work, but if you look at those individuals, many had resistance to start. We are now doing a study in the U.S. with 7-on/7-off, and in certain hands it works well, but you have to pick the right drugs and the right patients, with no background of resistance. But best is to keep the virus suppressed."

HIV Vaccines

Experts agreed that a preventive vaccine probably is still a long way off. Dr. Fauci said, "We certainly have not given up…Now, scientists are using very sophisticated molecular crystallization techniques to try to determine the correct epitopes (to target)…We didn't realize how easy it is for the virus to develop an escape route…At the end of the day, we will need a vaccine with a strong combination of an antibody-based approach and a cell body-mediated response…That's why it is so difficult."

A preventive vaccine has been tested in non-human primates with HIV to block disease progression. An expert described that as "a good temporizing approach," but he said it doesn't work in the long run.

The French ANRS group presented data in February 2003 on a therapeutic vaccine, but those were very preliminary results. An expert said, "It is a proof of concept of the possibility of inducing immune reactivity in patients treated with antiviral therapy." DermaVir, a transdermal therapeutic vaccine, is starting human clinical trials.

Other interesting points:

- More patients are being diagnosed with HIV at an advanced stage of disease, what is being referred to as "advanced naïve patients."
- **Hepatitis.** A hepatologist warned that HIV patients with HBV should always have their HBV treatment started at the same time as the treatment for HIV. It is not know yet whether it is also important to start HCV treatment early, and a trial is beginning to determine this.
- **Growth hormone.** There was no new data at IAS on the use of growth hormone to treat AIDS wasting, but an expert said, "There was intriguing data at the AIDS Conference in Barcelona showing low doses of growth hormone could lead to restoration of peripheral fat and correct some lipid abnormalities. That study needs to be followed, and lower doses of growth hormone tested. It is not clear where Ares Serono stands now on further studies, and Lilly is not doing any studies."
- **IL-2**. An IL-2 immune enhancer is not a vaccine, and the IL-2 story "still needs to be verified," an expert said. He also said the clinical relevance of IL-2 needs to be determined.

PROTEASE INHIBITORS

Protease inhibitors are a mainstay of HIV treatment, and sources agreed that they are not decreasing in importance. In fact, as much attention is being given to new protease inhibitors as to new classes of agents. A U.S. expert said, "PIs have been an important component of a treatment regimen since they were discovered. They have been shunted to second line, in part because of concerns about lipids, and in part because of confusion over what was causing the changes in fat distribution. It is reasonably clear now that the more disfiguring fat atrophy is almost certainly due to NRTI inhibitors and not PIs, though we are not sure how much PIs caused fat accumulation."

BOEHRINGER INGELHEIM'S Tripanavir

This non-peptide protease inhibitor is not approved yet in either the U.S. or Europe, but AIDS activists interrupted a Boehringer-sponsored symposium to protest the lack of availability of this drug, calling it a "tripanavir crisis." Protestors complained that clinical trial enrollment is completed and the entry criteria are too restrictive for the 600-patient compassionate use program. They also objected to waiting until September 2003 for the compassionate use program to start. A Boehringer official replied that there is a shortage of the drug right now, "We've had to pull the drug from clinical trials for the compassionate use program. We will expand manufacturing, but now all supplies are in the emergency program. All trial participants were guaranteed a continued supply of the drug, and as soon as more drug is available we will start the expanded access program."

Doctors did not appear excited about tripanavir. One commented, "The tripanavir data is confusing. Boosted looks less potent than Kaletra, but it is active against a wider range of strains." Another said, "I'm not sure of the long-term safety of tripanavir."

After a dose-finding study comparing 500 mg Tripanavir+100 mg ritonavir, 500 TPV/200r and 750 TPV/200r, the company chose to go forward with the 500 TPV/200r dose. A speaker said, "The 500 TPV/200r and 750 TPV/200r had similar antiviral activity…but it was clear that 500 TPV/200r had fewer adverse events, was better tolerated, and had fewer adverse-event discontinuations. Tripanavir requires ritonavir boosting – and requires more ritonavir than other PIs. An expert said, "This is the new drug furthest along in development right now. If Phase III is successful, it will be the next drug we have. The pattern of resistance we have in the Boehringer studies and issues about the fraction of patients with inadequate concentrations mean this drug will work for some patients. It's not a panacea, and there will be patients where it doesn't work."

BRISTOL-MYERS SQUIBB'S Reyataz (atazanavir)

Atazanavir is catching on in the U.S., and doctors predicted use will grow significantly. Several doctors who were asked to identify what they found most interesting or important at the meeting pointed to the atazanavir data. A Nevada doctor said, "It's a great medication. Head-to-head it is the same as Viracept, but it has better lipid control. It will expand the market and make doctors more comfortable with PIs because it is less cumbersome."

Atazanavir is expected to be approved in Europe by the end of this year, and European doctors also expect it to catch on well there. A Swiss doctor said, "It will be a big drug." Dr. Fauci called atazanavir a big advance, saying, "Atazanavir probably causes fewer metabolic abnormalities and doesn't share as many cross resistances with the other PIs." Another expert said, "Atazanavir is a more efficacious and more convenient PI. It is clear that it doesn't cause an increase in total cholesterol or triglycerides. The issue is whether atazanavir by itself, unboosted, is really as potent as Kaletra (Abbott, lopinavir)…Data here (at IAS) in treatment-experienced patients comparing boosted atazanavir to Kaletra found that, in patients with limited PI resistance, the two drugs looked quite comparable in activity. There has been no head-to-head trial of boosted vs. unboosted atazanavir or boosted atazanavir vs. Kaletra in naive patients, but it looks like boosted atazanavir will be equivalent to Kaletra."

Doctors were divided on whether or not it would become a first-line treatment. A U.S. doctor said, "EFV (Bristol-Myers Squibb's Sustiva, efavirenz) is still first line, not atazanavir." A French doctor said, "Atazanavir won't be the first PI that I use." An Italian doctor said, "Atazanavir will become first line in naïve patients."

Sales Outlook

The outlook is for atazanavir to decimate sales of Pfizer's Viracept, but it is also likely to take significant market share from Kaletra. On average, U.S. and European doctors estimated that within 12 months they would be using as much atazanavir as Kaletra in both naïve and experienced patients.

Comments by doctors included:

- *Maryland*: "Atazanavir will seriously cut into Viracept sales. I can't imagine why anyone would use Viracept. Atazanavir also will cut into Kaletra sales, but not replace it…At first, I will switch patients with lipid problems and see what my comfort level is with those patients."
- *Utah*: "Atazanavir is more effective in naive patients than we thought, and it is good boosted in experienced patients. It is looking very useful, and it is catching on…I will use it instead of EFV in some patients and in lieu of Kaletra in some."
- *New Hampshire*: "Atazanavir is not as effective as Kaletra in salvage, but it probably will replace Kaletra in first-PI patients."

- *Nevada*: "In a year, I'll be using as much atazanavir as Kaletra. Atazanavir has less of a track record than Kaletra. A really sick patient with an opportunistic infection and CD4<200 will get Kaletra, but an asymptomatic patient with CD4>200 who needs a first PI will get ATV, especially if lipids are an issue."
- *Colorado*: "Atazanavir will replace Kaletra, but I still favor Kaletra unless a patient already has lipid problems. We have more experience with Kaletra, and its resistance profile is good."
- *Texas:* "It is not on our formulary yet. If it gets one, I likely will use it, but I haven't figured out where, potentially in lieu of Kaletra."
- *California*: "A good chunk of Kaletra patients will try atazanavir first."
- *Italy #1*: "Atazanavir could be used more extensively than other PIs because of convenience and its lack of effect on lipids – but it may need to be boosted…In a year, I'll be using more atazanavir than Kaletra, and a lot less Viracept. Now, I use Viracept in naive patients, Kaletra in naïve patients with a high viral load, and Kaletra in experienced patients."
- *Italy #2:* "I will use ATV in place of Kaletra."
- *U.K.*: "It is potentially a big drug. The once-daily dosing and lipids are very attractive, but we need more data before it will really take off."

Yet, atazanavir may ramp slowly at first in the U.S. A U.S. doctor said, "It will take time for doctors to be comfortable with atazanavir." A California doctor said, "Atazanavir is a base hit, but not a home run."

Efficacy

Clinical trials have shown that unboosted atazanavir (ATV) is less efficacious than Abbott's Kaletra. However, speakers argued that the test tubes used in the 043 trial may have caused false conclusions to be drawn. They explained that PPT tubes were used for the atazanavir patients and EDTA tubes for the Kaletra patients, and they said the gel at the top of the PPT tubes may have affected the results, falsely elevating the viral load. One commented, "Atazanavir is not less effective than efavirenz, but maybe it is still less effective than Kaletra because that is boosted….Atazanavir will replace other PIs, and it may expand the market if boosted atazanavir shows, in trials, not to lose any efficacy."

Other experts said they suspect this argument is correct, but they still want to see it proven in a clinical trial comparing Kaletra and atazanavir, with EDTA used for all tubes. One said, "The tube explanation may be reasonable, but the study results are the study results, and I'd like to see the PPT study confirmed in just an EDTA tube study. We're left with some uncertainty on where to place unboosted atazanavir."

Pro atazanavir use:

- **QD dosing.** Right now, atazanavir has a big advantage with its QD dosing, but QD trials of Kaletra are underway, and one speaker said, "In the naïve population it looks like a good bet."
- **Less cross resistance.** A speaker said, "Atazanavir probably has fewer metabolic abnormalities and doesn't share as many cross resistances with the other PIs."
- **No increase in lipid levels.** Doctors were impressed with the lack of lipid effect with atazanavir. One said, "The lipids look very good." Another commented, "I see more and more patients for whom CHD risk is an issue…Kaletra is awesome virologically, but there is a potential for lipid abnormalities. Kaletra advantages are durability and power, and it is forgiving with non-adherent patients, but atazanavir's advantage is lipids."

However, doctors generally believe that treating the HIV is more important than worrying about lipids, but for patients whose lipid levels already are high or who are at risk of coronary heart disease, atazanavir is likely to be the protease inhibitor of choice. An expert said, "The lipid difference between the two (atazanavir and Kaletra) is mostly a marketing gimmick. If I have to choose a protease inhibitor, I will use Kaletra, unless the patient is really at risk of CHD, and then I might use atazanavir." Another expert said, "With some patients at risk of CHD, PI lipid elevations might be a consideration, but it is not the key factor for most patients." A third source said, "Lipids and CHD are not on the radar screen of most patients." A fourth commented, "Antiviral activity is more important than lipids."

48-Week Results of the Metabolic Substudy (BMS-034) of Atazanavir

Measurement	**ATV 400 mg QD** n=111	**EFV 600 mg QD** n=100
Visceral adipose tissue (VAT)	50	75
Subcutaneous adipose tissue (SAT)	150	170
Total adipose tissue (TAT)	205	245
Appendicular, truncal and total body fat (by DEXA)	.42	.42 app
VAT:TAT	-.03	+.02
VAT:SAT	+.06	N/A
TC	No change	Increase
LDL	No change	Increase
HDL	No change	No change
TB	Slightly higher with ATV	N/A

A 48-week substudy of the effect of atazanavir on metabolism found that both ATV and EFV are associated with comparable and proportional effects on body fat distribution. The pattern of fat increase was consistent with successful disease treatment. ATV treatment did not result in an increase in total cholesterol, fasting LDL or fasting trigylcerides. Neither ATV nor EFV resulted in an increase in insulin resistance indices.

Con atazanavir use:

- **Increased bilirubin** in a significant number of patients, some of whom develop jaundice. However, only one trial patient withdrew from clinical trials due to this, and that was in a patient getting atazanavir boosted with ritonavir. Doctors questioned about the jaundice/bilirubin issue, generally were not worried about it. An Italian physician said, "It is not a big concern. I've managed the same issue with indinavir (Merck's Crixivan) without major problems." A U.S. doctor said, "Jaundice is not a concern; it won't prevent my use." A Utah doctor added, "It is not a big deal. Indinavir had the same issue."
- **Less data.** Doctors have more experience with Kaletra. One expert commented, "Atazanavir may not be less effective than Kaletra, but I have more experience with Kaletra."
- **Efficacy** may be less than Kaletra unless atazanavir is boosted with ritonavir, though this issue is being reviewed and some sources believe they may turn out to be comparable.

To boost or not to boost?

Doctors generally agree that boosted atazanavir is preferable in treatment-experienced patients, but there is no consensus on whether to boost atazanavir in naïve patients. Asked about the role for unboosted atazanavir, a speaker said, "There is no data on using boosted atazanavir in naïve patients, but it would be logical to do that study. Do you need the data to use it clinically? That is a doctor decision. It is a high priority to do the research. If unboosted atazanavir is as potent as boosted Kaletra, is there a potential advantage to using unboosted atazanavir?" A New Hampshire doctor said, "I won't boost it in naïve patients until there is more data, but I will boost it in experienced patients."

Arguments in favor of boosting:

- Texas: "I'm tempted to use it boosted from the get-go, especially in experienced patients, but also in naïve patients, though they may develop lipid problems later, especially when boosted."
- Utah: "Boosted is expensive for sure, but I probably will boost it in naïve patients. You don't give up a log of the benefit with boosting, but you give up some, and there is no data."
- U.S.: "I'll use boosted atazanavir in naïve patients."
- Maryland: "I will boost it in naïve patients. Atazanavir is less effective (than Kaletra) unless boosted, so you need to boost it."
- U.K.: "About 15%-20% of patients have hyperlipidemia problems with Kaletra, and switching them to atazanavir would be an option. Atazanavir is less effective than Kaletra unless it is boosted, so you will need to boost it. A lot of patients are happy with Kaletra because it is working. But you could start some patients on atazanavir."
- Switzerland: "I think boosted will win the day."

Arguments against boosting:

- A U.K. doctor said, "I'll only use unboosted atazanavir in naïve patients because of the lack of data on boosted atazanavir."
- An Italian doctor said, "I won't boost atazanavir in naïve patients, but it is not very potent unboosted, so in patients with a high viral load it could be useful to boost it for the first few weeks (4-12 weeks), and then drop the ritonavir."
- A Nevada doctor said, "I'll use it unboosted. Boosting defeats the purpose. I will not boost it in non-salvage patients. There is no PK data on boosting it in native patients."

Sources all agreed that boosted atazanavir is equivalent to Kaletra in efficacy, has a more favorable lipid profile, and causes less diarrhea. A speaker said, "What we see clinically is more similarity than differences…Boosted atazanavir is effective for (1) Treatment naive patients, similar to Bristol-Myers Squibb's Sustiva (efavirenz, EFV, EFZ), and (2) Treatment-experienced patients, similar to Kaletra." Another speaker said, "Some doctors only use a boosted protease inhibitor (PI) when a PI is selected…but others are not comfortable with boosted PIs…This drug may be amply potent even unboosted…and in experienced patients, it may do other things, like decreasing resistance at rebound. Some doctors have decided boosted atazanavir is an option in naïve patients – even though there is no study data on that, though they can extrapolate."

When boosted atazanavir (ATV/r) is used, Bristol-Myers reportedly will recommend using 300 mg atazanavir with 100 mg of ritonavir (Abbott's Norvir), not Gilead's Viread (tenofovir). Asked whether he would use boosted atazanavir in naïve patients, a U.S. expert said, "Atazanavir+ritonavir (boosted atazanavir) is probably a good regimen for first line, but I would still reserve it for second line after a non-nucleotide had failed. There is not enough data to recommend it for first line yet."

Combining atazanavir with Viread

Boosted atazanavir ***can*** be given with Viread. Combining atazanavir with Viread reduces the concentration of atazanavir significantly, so the atazanavir dose must be boosted (with ritonavir) to compensate for this. An expert said, "Viread is likely to be one of the more widely used nucleotides, but it reduces atazanavir concentrations by 30%-40%, so you almost have to boost atazan-avir if you combine them." Another expert said, "When you combine atazanavir and Viread, you have to add a mini dose of ritonavir to boost the atazanavir. Then, there is no loss of efficacy." A third source said, "You have to change the dose of atazanavir if you combine it with Viread." A fourth doctor added, "Gilead thinks that if Viread is added to atazanavir, the atazanavir needs to be boosted."

Switching from Another Protease Inhibitor to Atazanavir

A poster presented 4-week results from an open label trial that switched 22 patients from PI-based HAART administered BID to atazanavir administered QD. Researchers concluded that atazanavir maintained virologic suppression and the immunologic response, increased lipid levels, and results in 99.5% adherence.

Measurement	Patients switched to Atazanavir
Adherence	
No missed doses	15/22
≤1 missed dose/month	5/22
≥2 missed doses/month	2/22
Virology (patients with <50 copies)	
Among completors	8/18
Among non-completors	¾
Among non-completor failures	¼

Unboosted Atazanavir Data

Results were presented from the 24-week, randomized BMS A1424-043 Study comparing unboosted atazanavir to Kaletra in patients who have experienced virologic failure with prior PI agents. Researchers found a 0.3 log greater reduction in HIV RNA with Kaletra than atazanavir. Atazanavir had a better lipid profile but an increase in bilirubin, which caused one discontinuation.

BMS Study A1424-043: Unboosted Atazanavir vs. Kaletra

Measurement	Atazanavir 400 mg QD +2 NRTIS	Kaletra 400 mg BID +2 NRTI
Number of patients	144	146
Virus susceptibility	72% to ATV	86% to Kaletra
Discontinuations prior to Week 24	7%	7%
Discontinuations due to adverse events	<1%	3%
Primary endpoint #1: RNA mean change from baseline	7 log drop (p=.032)	2 log drop
Primary endpoint #2: **Lipid Effects**		
Total cholesterol change from baseline	-2%	+17%
LDL change from baseline	-6%	+5%
HDL change from baseline	+12%	+18%
Use of any lipid lowering agent	2% prior 5% end of study	1% prior 19% end of study
Secondary endpoints		
Viral load <400	59%	77%
Viral load <50 copies	38%	54%
Baseline predictors of response		
Exposure to one prior PI	63%	N/A
Exposure to ≥2 prior PIs	48%	N/A
No NRTI mutations	65%	N/A
≥1 NRTI mutation	58%	N/A
Safety		
Total adverse events	17%	23%
Headache	4%	3%
Jaundice	3%	0
Diarrhea	1%	3%
Lipodystrophy	3%	1%
Total bilirubin	22%	0
ALT elevated	6%	1%
AST elevated	3%	1%

BMS Study A1424-045: Boosted Atazanavir vs. Other Protease Inhibitors

Measurement	QD ATV 300 mg + ritonavir 100 mg +QD Viread 300 mg + 1 NRTI	QD ATV 400 mg + SQV 1200 mg +QD Viread 300 mg + 1 NRTI	BID Kaletra 400 mg + ritonavir 100 mg +QD Viread 300 mg + 1 NRTI
Number of patients	120	115	123
Resistance at baseline	30% to ATV	N/A	15% to Kaletra
Discontinuations	6%	12%	5%
Primary endpoint: HIV RNA reduction from baseline	-1.86 $\log_{10}$	-1.52 $\log_{10}$	-1.89 $\log_{10}$
Patients with HIV RNA <400 copies/mL	64%	44%	62%
Patients with HIV RNA <50 copies/mL	39%	23%	42%
CD4 change from baseline (cells mm^3)	83	59	90

BMS Study A1424-045: Boosted Atazanavir vs. Other Protease Inhibitors

Measurement	ATV 300 mg QD + ritonavir 100 mg +QD Viread 300 mg + 1 NRTI	ATV 400 mg QD + SQV 1200 mg +QD Viread 300 mg + 1 NRTI	Kaletra 400 mg BID + ritonavir 100 mg +QD Viread 300 mg + 1 NRTI
Lipid Effects			
Total cholesterol change from baseline	-8%	-9%	+3%
LDL change from baseline	-10%	-11%	-4%
HDL change from baseline	+7%	+1%	0
Use of any lipid lowering agent	6 prior 7 on study	7 prior 12 on study	5 prior 15 on study
Adverse Events			
Total	22%	26%	22%
Diarrhea	3%	5%	11%
Jaundice	6%	2%	0
Nausea	2%	7%	2%
Scleral icterus	3%	0	0
Total bilirubin	45%	19%	<1%
ALT elevated	3%	4%	3%
AST elevated	3%	2%	<1%

Boosted Atazanavir Data

Researchers presented a 24-week interim analysis of a 48-week study comparing boosted atazanavir to Kaletra and to the combination of atazanavir and SQV in patients who have experienced virologic failure with prior PI agents. In terms of efficacy, ATV/4 was fairly equivalent to Kaletra, but both were superior to ATV+SQV. There was a high incidence of elevated bilirubin and jaundice with ATV/r, but no patients withdrew due to this, and researchers claimed it was not clinically significant because liver enzymes were not elevated. However, ATV/r had the best lipid profile.

GLAXOSMITHKLINE/VERTEX'S Telzir (fosamprenavir, GW-433908, VX-175, known as "908")

This is a prodrug of Glaxo's Agenerase (amprenavir). There wasn't much excitement about this drug with atazanavir slightly ahead, and it has no lipid advantages over Kaletra. "908" was submitted to the FDA in December 2002. It is two pills to taken twice a day, but 48-week data from two trials in naïve patients were presented at IAS.

48-Week Results of NEAT and SOLO

Measurement	908 in NEAT	908 in SOLO
Incidence of primary and sedondary mutations at the first time point after therapy failure (typically 12 weeks)	31% (8/26 patients)	50% (27/54 patients)

The NEAT trial compared the safety and efficacy of 908 BID to NFV BID, and the SOLO trial compared boosted 908 (GW-433908/r) to NFV BID. All subjects received abacavir plus lamivudine BID.

Shortly after the IAS meeting, Vertex announced that the Phase III CONTEXT trial failed to meet its primary endpoint of a non-inferior time-averaged change in viral load from baseline: 58% of patients taking BID Telzir/r had a viral load <400 copies/mL compared to 61% of Kaletra patients. This open-label trial compared boosted Telzir (both BID and QD) in 320 treatment-experienced patients with prior virologic failure at 24 and 48 weeks.

JOHNSON & JOHNSON'S TMC-114

Several experts pointed to this protease inhibitor as one of the more promising drugs in development. One expert said he thinks this PI looks more promising than Boehringer Ingelheim's tripanavir, saying, "It probably is more potent and active against a wider range than tripanavir, but it has been tested in only a handful of patients so far. There are still issues of formulation and dosing that need to be worked out."

Data from a 14-day trial of boosted TMC-114 (TMC-114 plus ritonavir) was presented as a Late Breaker. Use of Kaletra was not indicative of a response to TMC-114, and TMC-114 susceptibility at baseline was not predictive of virologic response. Two patients dropped out. There was one serious adverse event, an hepatotoxicity, and a researcher said, "It was difficult to understand the causality because it occurred on Day 12 and seemed to increase when treatment was discontinued, but there were many confounding factors in this patient, including alcohol and concomitant ARVs." The next step for TMC-114 will be a Phase IIb program, a dose-finding program in North American and Europe, which is to start in 4Q2003.

Other protease inhibitors in development include:

- **GlaxoSmithKline's GW-640385**, a third generation protease inhibitor in Phase I development.
- **Roche's RO-033-4649**, which is in Phase I development.
- **Merck's L-756,423**
- **Gilead's Mozenavir** (DMP-450)

14-Day Results of TMC-114/r

Measurement	No protease inhibitor	300 mg TMC-114 + 100 mg ritonavir BID	600 mg TMC-114 + 100 mg ritonavir BID	900 mg TMC-114 + 100 mg ritonavir QD
Change in $\log_{10}$ viral load	+.02	-1.24	-1.13	-1.50
HIV RNA decrease >0.5 $\log_{10}$	25%	100%	92%	100%
HIV RNA decrease >1.0 $\log_{10}$	18%	70%	70%	92%
Diarrhea	N/A	32%		
Flatulence	N/A	18%		
Headache	N/A	16%		
Dizziness	N/A	11%		

ENTRY INHIBITORS

Dr. Robert Gallo, one of the co-discoverers of HIV, described entry inhibitors as an extremely attractive new approach. He said, "I think they are the most attractive new approach for some time to come. Fuzeon is the first entry inhibitor and the first fusion inhibitor."

ROCHE/TRIMERIS'S Fuzeon (enfuvirtide, T-20)

Fuzeon was approved in the U.S. on March 13, 2003, and in Europe on May 27, 2003. Roche and Trimeris gave Fuzeon a big push at this meeting. Several leaders in the field gave it high praise, and doctors said they are very happy to have it in their armamentarium. Dr. Fauci described Fuzeon as very promising, "T-20 was a breakthrough drug. It is very important because it is the first drug that enters into realm of a new target…Obviously, administration needs to be improved. We need an oral version; that would be very exciting…It's good for patients who have failed other regimens. As we gain more experience, it will gradually be used more as a primary tool…If it continues to do well…it is likely to advance to center stage reasonably soon." Another expert said, "It is also for patients with side effects to other drugs."

Yet, Fuzeon is unlikely to become more than a niche product. There is no pent-up demand for Fuzeon, no waiting list, and few patient requests for the drug. The injections are ***much*** more of a problem than the companies indicate, and cost is dampening use. Even in European countries or with 100% reimbursement or under U.S. health plans with full coverage, doctors are planning to use Fuzeon only selectively, and they do not expect usage to continue to increase after the initial ramp. In 12 months, sources estimated that an average of less than 6% of their patients would be on Fuzeon, and they don't expect that market share to change over the next year, so in 24 months <6% of patients are likely to be on it.

Roche and Trimeris officials said they would like to see Fuzeon used as early as possible, ideally second line, while there are still several other agents that work with which it could be combined. Fuzeon works in salvage patients who are resistant to all other drugs, but it works better when combined with an active agent. A researcher said, "Fuzeon has a 0.7 log effect if there is nothing to partner it with, but adding other drugs increases its results."

However, doctors questioned about the outlook for Fuzeon use all insisted it should be reserved for third or fourth line therapy. They acknowledged that it should be used before patients become refractory to everything else, but they want to wait as long as possible to use it. Among comments doctors made about Fuzeon were:

- *Massachusetts*: "T-20 will be a niche product due to reimbursement, patient resistance to the injection site reactions, and patients' choice of what to use."
- *New Jersey*: "I haven't used it yet. I ***may*** use it in the future, but there is not waiting list or patient demand for it."
- *Texas*: "I haven't used it yet, and I may still not have any patients on it in a year. There are only a small number of patients for whom this is appropriate…A lot of patients ask about it who don't need it. It got a lot of hype, but the perception is that it is more than it is. This is a very nice product."
- *Utah*: "I will use T-20 in salvage patients, but it is not second-line. Patients who really need it and can stick themselves want it, but there is not a clamor for it."
- *Nevada*: "I will try it in every refractory patients. It is good to add if there is only one drug left that works."
- *Maryland*: "There is no shortage, but that could happen if it were added to all formularies."
- *Pennsylvania*: "It is expensive and difficult to use, and the pneumonia rate is high."
- *Netherlands*: "T-20 will be a niche product and will have a lot of problems…It is a very difficult drug."
- *Italy:* "It is quite inconvenient for patients, and the price will make doctors careful about using it. There is no waiting list for T-20."
- *Canada*: "It is not all that great a drug, but it is more durable than some of us thought…I hope patients don't fail other regimens so they don't have to go to this…If it were oral, it would be huge, maybe even front-line. If it is moved earlier, the companies will have to supply and price it for developing countries, and that could be problematic for them."

- *U.K.*: "Use will grow, but it won't be as big as EFV or Kaletra."
- *Switzerland:* "In its current form, it won't be widely used because of cost, injections and the other drugs available."

Thus, sources predicted Fuzeon will be a niche, probably a very niche, product. None of these sources have had any supply problems, there is no waiting list for the drug, and no doctor believes supply will be a problem. One said, "We have a bunch of patients on it already – about 1%-2% of all our AIDS patients. In a year, I think about 5%-10% will be on it, and that is partly because it is injectable, partly because of cost, and partly finding the right patients eligible for it. In two years, it will probably be about the same number – 5%-10% still. The dilemma is finding the right time to give it. You don't want to give it too late but not too early either when you could get good suppression with other drugs."

Although demand is the issue, not supply, Roche and Trimeris announced that they are increasing the supply of Fuzeon from 12,000-15,000 patients to 18,000 by the end of 2003. A Roche official said, "This is the most complex drug ever produced at this scale. There are 137 steps involved in production."

The factors affecting use of this drug include:

- **Cost**. Even where the drug is fully reimbursed, doctors expressed concern about devoting so much of the financial resources to this drug and said they are and will be very selective in the patients for whom they prescribe it. A cost-effectiveness analysis of T-20 by researchers at Brigham & Women's Hospital in the U.S. compared T-20+ OBR (optimized background regimen) to OBR alone. They found Fuzeon increased the quality of life and life expectancy by 17.9 vs. 14.9 for OBR alone. The incremental cost over OBR alone was $102,300 for Fuzeon. A California doctor said, "At $20,000, you want to use it in the right patients."

Procedure	Cost per QALY gained
Hemodialysis for critically ill patients	$169,000
INF-α for CML	$108,200
Fuzeon	$102,300
Bone marrow transplant for CML	$61,900
CABG	$32,300

- **BID subcutaneous injections**. These are not like insulin injections; the volume is much larger, and they cause large and unsightly nodules. Sources cited this, even more than cost, as a reason the drug will be used in only a very select group of patients. One doctor said, "The T-20 injections are a big problem – more than is being discussed here (at IAS)." Another commented, "The only popular injectable drug is heroin." A Nevada doctor added, "Injections are not that big an issue when patients are desperate, but they are more problematic if they try to use it earlier." A Swiss doctor said, "In Europe and North America, a lot of HIV patients are drug users, so injecting is not a good idea."

- **Injection site reactions**. The reactions are hard nodules at the injection site and sometimes large (3 in.) red blotches, and these reactions last a very, very long time (often months). An expert said all patients get site reactions at some point, "The site reactions have not been a common cause of trial dropouts, but they are certainly bothersome…BID is a disadvantage." A researcher said, "Injection site reactions occur in about 98% of patients, but only 3% stop treatment as a result….Generally the reactions are mild to moderate."

- **Resistance**. Experts agreed that resistance to Fuzeon does develop over time, particularly if it is used alone. One said, "It is very difficult to avoid resistance." Another expert said, "We haven't seen any resistance yet. We aren't measuring it outside of trials, but we are doing it as part of a research study, and there has been resistance described. At the Retrovirus Conference (February 2003) there was data presented. T-20 failures showed resistance mutations accompanied by a shift to a more resistant virus. So, clearly, resistance develops. That is a reason to use it earlier – but other reasons (cost and injections) keep it from being used earlier."

  Patients who develop resistance may still be kept on Fuzeon. A company official said, "Many people who met the criteria for Fuzeon failure decided to stay on the drug anyway." A California doctor said, "Patients may fail within a year, but they may still stay on it if they feel better."

- **Reimbursement**. European coverage is pretty good, according to doctors. In the U.S., Medicaid covers Fuzeon in every state, an increasing number of private carriers are covering it, and Roche and Trimeris are making progress in getting ADAP (AIDS Drug Assistance Program) coverage. A U.S. doctor said, "So far, reimbursement has been reasonable." A U.K. doctor said, "The availability (for patients) in any country will depend on reimbursement. NICE hasn't done HIV drugs yet (and probably won't before 2005), and the cost-effectiveness analysis of T-20 is okay."

- **Bacterial pneumonia**. An increased rate of bacterial pneumonia in Fuzeon patients has been seen, but company officials said the rates are similar to that reported in people living with HIV. Another official said, "We don't have a direct explanation. We looked at individual cases, and some had documented bacterial pneumonia, but not all."

- **Other new drugs.** As more new drugs become available, doctors believe the need for Fuzeon will decrease. A California doctor said, "The array of drugs available now is

extraordinary. I will use T-20 for failing patients and those with pancreatitis, but probably not often." A Maryland doctor said, "With tripanavir and other drugs coming, I may be using less in two years than I will be using in 12 months."

TORO-1 (U.S., Canada, Mexico, and Brazil) and TORO-2 (Europe and Australia) were randomized, open-label trials of about 1,000 patients at 112 centers internationally. Patients were on a background of three to five other drugs.

Pooled Analysis of TORO-1 and TORO-2 Trials

	24 Weeks		48 Weeks	
Measurement	**Fuzeon n=661**	**Optimized Therapy n=334**	**Fuzeon n=661**	**Optimized Therapy n=334**
≥1 log decline	47.2%	24.9%	37.4%	17.1%
<400 copies/mL	32.7%	15.0%	30.4%	12.0%
<50 copies/mL	15.9%	6.3%	18.3%	7.8%
CD4 cell count (mm^3)	71	35	91	45
Median time to virologic failure	---	---	32 weeks	11 weeks
Adverse Events				
Injection site reactions	N/A	N/A	98%	N/A
Discontinuation due to injection site reactions	N/A	N/A	4%	N/A
Fatigue	15%	17%	24.1%	37.6%
Nausea	19%	23%	27.1%	50.0%
Diarrhea	27%	33%	37.7%	73.4%
Headache	15.8%	19.7%	N/A	N/A
Vomiting	15.1%	27.5%	N/A	N/A
Pyrexia	14.0%	24.1%	N/A	N/A
Peripheral neuropathy	15.4%	13.6%	N/A	N/A

TRIMERIS'S T-1249

This once-daily injection is a follow-on to Fuzeon (T-20). It was described as a "completely different molecule" from Fuzeon. A proof-of-concept study indicated it works in some Fuzeon resistant patients. An expert called it a "modest advance over Fuzeon." Sources all agreed it appears to work in Fuzeon failures, and, at this point, it is being positioned for that market, not as a replacement for Fuzeon.

Other entry inhibitors in development include:

- **PROGENICS' PRO-542.**
- **BRISTOL-MYERS SQUIBB'S BMS-806**
- **TANOX'S TNX-355.** Several sources mentioned this as particularly promising. It is either a once every other week or once every three week injection.

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIS)

GILEAD'S Viread (tenofovir disoproxil fumarate)

Viread is very popular and use is still growing. A U.S. physician said, "I love it. It is useful at every stage I've given it. It is a great salvage drug, and it is good for patients with HBV, but not HCV). I use it front-line sometimes because it is quite potent in patients who can't tolerate other nukes or have a sky high viral load. And it is good for squirrelly patients who come to treatment late. Use is still expanding." A California doctor said, "It is starting to take off. It is safe, has few side effects, no cross-resistance, and is once a day. All that is appealing." A Utah doctor said, "It is in a more mature phase, but use is still growing."

Renal toxicity is real, and it is something doctors are watching, but doctors are not worried about it. In clinical trials of Viread there was a low incidence of renal toxicity (elevated creatinine) and no discontinuations for increased creatinine or decreased phosphorus. Out of 587 patients, Gilead reported 32 patients (5%) with a grade 1 increase in renal toxicity, but no cases of Grade 2, 3 or 4.

There have been post-marketing reports of renal toxicity, and three cases of Fanconi Syndrome were reported at the Retrovirus Conference in February 2003 (all from the same clinic in France). A U.S. expert (a speaker at a Gilead-sponsored symposium) said, "We are seeing some renal toxicity in clinical use of Viread. It is not a serious concern, but it needs to be watched." Another expert said, "We haven't seen any renal toxicity yet, and no rhabdomyolysis." A California doctor said, "It is dose-related and duration-related." A Utah doctor added, "The renal toxicity is no surprise, but it makes me more comfortable to see the drug have a toxicity."

Canadian researchers presented data at the IAS meeting indicating there is a small but real renal toxicity issue with Viread. The researchers did a retrospective analysis of 563 patients taking GlaxoSmithKline's Ziagen (abacavir, ABC) with or without Viread. They found 11 patients (5%) discontinued Viread between months 2 and 18 (median 6 months) due to creatinine increase. Nine of these patients were biopsied, and all showed acute tubular injury. Two patients had to be hospitalized. In all, creatinine decreased after Viread was discontinued. The speaker said, "My nephrology colleagues did feel there was no evidence of Fanconi syndrome in the patients who stopped taking Viread."

A Gilead official pointed out that the creatinine level in the Canadian patients resolved in most patients who stayed on the drug without any sequelae, but a researcher responded that the Viread follow-up may have been too short to see enough problems develop to cause dropouts, "It is correct that they

either resolved or stayed mild enough not to merit a discontinuation…Our nephrologists said it was not like Fanconi Syndrome, though on biopsy they had proximal tubular necrosis, so it is hard to know the pathological association. Many did not have progressive dysfunction, but we did have short follow-up on some of these patients. It may not have progressed in two or three months, and we don't know what is going to happen with longer follow-up." Asked about this data, other experts at the meeting said they were not concerned with renal toxicity, though they will continue to keep an eye on this issue.

Canadian Viread Renal Toxicity Study

Measurement	Viread n=310	Ziagen n=424	p-value
Primary endpoint: Creatinine ≥1.5 baseline	91.6%	96.4%	p=<.001
Months of follow-up	4.1	11.9	p=<.001
Elevated creatinine in patients with normal baseline phosphorus	23.0%	21.4%	Nss

Miscellaneous

- A poster reported on a study that found that adding low dose (250 mg) ddI to Viread is as effective as higher dose ddI (400 mg) but better well-tolerated.
- Bone fractures do not appear to be a problem out to 96 weeks with Viread.

GILEAD'S Emtriva (FTC, emtricitabine, formerly known as Coviracil)

Doctors were underwhelmed with FTC. All agreed it is comparable to 3TC, but few saw much reason to switch patients from 3TC to it, since both drugs are available in QD formulations. However, most believe it will eventually catch on, particularly if it is combined with Viread in a single pill. A French doctor estimated he would have 12% of his AIDS patients on it in a year. An Italian doctor thought he'd be using half 3TC and half FTC within a year, but he has no plans to switch patients from 3TC to FTC. A Utah doctor said, "I'll probably split my use between FTC and 3TC to gain experience, but I won't switch patients."

Emtriva (Study 301) Results at 60 Weeks

Endpoint	Emtriva (FTC) n=286	Zerit (d4T) n=285	p-value
Persistent suppression of HIV RNA <400 copies/mL	79%	63%	p<.0001
Mean increase in CD4 cells/mm^3	165	137	Nss
Permanent discontinuation of study medication due to clinical adverse events	7.4%	16.6%	p=.003

A 60-week, 571-patient Phase III trial comparing once-daily FTC to twice-daily d4T (Bristol Myers Squibb's Zerit, stavudine), in companion with other antiviral medications. Based on an interim analysis, the DSMB recommended that the trial be unblinded and all patients offered FTC due to its superiority on both primary and secondary endpoints. There was less nausea, diarrhea, abnormal dreams, parathesia, neuropathy, symptomatic hyperlactemia and lactic acidosis with FTC.

A 24-week, 37-patient comparison of first-line therapy with FTC and twice-daily abacavir (GlaxoSmithKline's Ziagen), in combination with other antiviral agents.

FTC vs. Abacavir at 24 Weeks

Endpoint	Emtriva (FTC) n=18	Ziagen n=19
Reduction in HIV RNA <50 copies/mL	83%	63%
Mean increase from baseline in CD4 cells/mm^3	8%	6%
Discontinuation due to clinical adverse events	2 patients	2 patients

Sources questioned about the outlook for FTC all agreed that it will have little use, or at a minimum ramp very slowly, unless and until it becomes available as a combination pill with Viread. A speaker at a Gilead-sponsored symposium was asked if there are any clinically relevant differences between 3TC and FTC, and he commented, We don't have that answer…There is no trial comparing FTC and 3TC once-daily. The profiles are similar, but we need clinical trials to see if there is a difference. I think the difference might be small if any." Another source said, "A tentative analysis suggests that resistance emerges more slowly with FTC, but we have to wait and see if that is proven."

GILEAD'S Combination FTC/Viread

Doctors were very enthusiastic about this combination, and most believe it will do very well when it is available. A French doctor said, "It will be big." A Dutch doctor said, "The combination will go up-front." A California doctor said, "I will only use FTC in combination (with Viread)." A Utah doctor said, "The combination will make patients happier and increase compliance. 3TC's only remaining advantage is experience." A U.K. doctor commented, "FTC will only take off if it is offered as a combination."

A Gilead official said (a) the IND for a combination pill (Viread/FTC) was filed, (b) a trial is due to start shortly (if it hasn't already started), and (c) the company hopes to submit the NDA in 2Q04. The trial will be Viread vs. Viread/FTC, and although the FDA has approved the trial design, there is

no Special Protocol Assessment. An expert commented, "The combination will be good, but it is a long way off."

Although other combinations pills have had difficulty getting FDA approval even when two approved drugs are combined (e.g., Pharmacia's Xalcom), this appears to be less of a problem with HIV drugs. Sources were all confident that a combination Viread/FTC pill will not have a higher bar than other HIV drugs, such as GlaxoSmithKline Combivir (AZT/3TC, lamivudine/zidovudine).

Doctors are eager for combination of Viread/FTC. Most sources indicated they would feel very comfortable switching to the combination, though patients who fail on FTC or on the combination won't get any benefit from a switch to 3TC.

There was no negative news for the combination product – no data indicating lipodystrophy or mitochondrial problems. Doctors do not believe combining the two drugs will create any problems not seen with each individual drug.

SHIRE'S SPD-754

Results were presented from a double-blind, placebo-controlled, randomized French study (#093) of SPD-754, a cytidine analog NRTI, as monotherapy. Four doses and both BID and QD administration were studied in 64 patients. It was a small, short study, but the data looked good. There was a trend toward an improvement in CD4 count, but it was not statistically significant. All doses were well tolerated, with all adverse events mild to moderate, no serious adverse events, and no withdrawals due to adverse events.

Study 093 Results with SPD-754

	1600 mg BID	1200 mg BID and QD	800 mg BID and QD	400 mg BID	Placebo
Mean change in viral load at Day 10	-1.5	-1.64	-1.40	-1.18	---
>1 log reduction in viral load	92%	86%	75%	64%	0
Headache	8%	6%	4%	3%	6%

Other NRTIs in development include:

- **MEDIVIR'S alovudine** (MIV-310). An expert said this was abandoned for hepatotoxicity, but it may still go forward at lower doses, which were quite effective in multi-resistant patients.
- **PHARMASSET PHARMACEUTICALS' Reverset** (D-D4FC, formerly DPC-817).
- **ACHILLION PHARMACEUTICALS' ACH-126,443** (Beta-L-Fd4C).

NON-NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIS)

The most popular HIV drug right now appears to be Bristol-Myers Squibb's Sustiva (efavirenz, EFV). Doctors had very high praise for this indeed. A Texas doctor said, "EFV is clearly the hottest drug right now, but any new PI could change that a little. The bottom line for me is using a PI at some point, using an NRTI at some point, and it is not clinically important which a patient takes first. Simplifying the regimen is important, but so is the price."

NNRTI's in development include:

- **SARAWAK MEDICHEM PHARMACEUTICALS' Calanolide A**
- **PFIZER/AGOURON'S Capravirine** (AG1549)
- **BRISTOL-MYERS SQUIBB'S DPC-083**
- **MEDIVIR'S MIV-150**
- **GLAXO SMITH KLINE'S GW-678248.** This was discovered in-house at Glaxo.
- **JOHNSON & JOHNSON/TIBOTEC'S TMC-120** and **TMC-125**

OTHER DRUGS IN DEVELOPMENT

Integrase inhibitors

An expert said, "Merck has made substantial progress in this area and has ongoing trials, but it is still the early stage, and we are waiting to see how they do." Another expert said, "I think Merck's drug is dead. They haven't formally buried it, but the word is it will be shelved in favor of another integrase inhibitor." A third source said, "We are still struggling with integrase inhibitors. That is a nut to crack that we haven't done." An expert from the Netherlands said, "CCR5 are proving difficult compounds – and they are injected. What we need is a new, simple, once-weekly agent." Another expert said, "Merck is still working on integrase inhibitors, and Glaxo bought a Japanese company that has one."

BIOALLIANCE PHARMA'S BA-011, a pre-integrase inhibitor, may be worth watching. It is a new class, and complementary to L-731,988, an anti-IN compound.

CCR5 blockers

There was no new data at IAS on these, but an expert said there is a lot of interest and excitement about them, "Personally, I see them more likely to be useful for early rather than later therapy, but that is controversial. Many people hope they will be useful in salvage." These include:

- **TAKEDA'S TAK-220**.

- **GLAXO SMITH KLINE'S 873140**. This recently entered Phase I trials.
- **SCHERING PLOUGH'S SCH/C** and **SCH/D**. These reportedly are the only CCR5 inhibitors to have demonstrated activity in humans so far. A source said SCH/C may be abandoned in favor of SCH/D. Another source said the Phase II data on these agents looks good, "This is the best drug story). It's oral instead of an injection."
- **PFIZER'S UK-427,857**.
- **ONO'S AK-602**.

Maturation inhibitors

Actelion is working on one of these, and a source said it "looks good," but there was no new data on it at IAS.

MISCELLANEOUS

Clinical Trials Book

Dr. G. Schreij, an infectious disease specialist at the University of Maastricht in the Netherlands, has written a book **The HIV Trial Guide: A Guide to Major Studies, Trials and Acronyms of HIV AntiRetroviral Therapy 1985-2003**, This very helpful book lists all the clinical trials in HIV – the new ones and the old ones. It cites the authors, abstract citations, trial design, and much more. He said, "I started working on this in 1994 because I felt many of my colleagues were not aware of all the HIV trials. The pharmaceutical companies push only the ones in their own area. There are few people with an overview."

Boehringer Ingelheim gave Dr. Schreij an unrestricted grant to do the book, and Boehringer gave out 5,000 copies of the newest version, the second edition, at the meeting. Dr. Schreij said doctors seemed very enthusiastic about the book, and he plans to update the data and do a new edition every year. He donates all his royalties to HIV research.

Approved Drugs

A good website for HIV drugs is: www.aidsinfonet.org, Fact Sheet 402. ♦

Guide to Approved HIV Drugs

BRAND NAME	Generic name	Acronym	Manufacturer	Class
Agenerase	Amprenavir	APV	GlaxoSmithKline	PI
Combivir	Lamivudine/zidovudine	AZT/3TC	GlaxoSmithKline	NRTI
Crixivan	Indinavir	IDV	Merck	PI
Emtriva	Emtricitabine	FTC	Gilead	NRTI
Epivir	Lamivudine	3TC	GlaxoSmithKline	NRTI
Fortovase	Saquinavir	SQV	Roche	PI
Fuzeon	Enfuvirtide	T-20	Roche/Trimeris	Entry Inhibitor
Hivid	Zalcitabine	DdC	Roche	NRTI
Invirase	Saquinavir	SQV	Roche	PI
Kaletra	Lopinavir+ritonavir	LPV/r	Abbott	PI
Norvir	Ritonavir	RTV, /r	Abbott	PI
Rescriptor	Delavirdine	DLV	Pfizer/Agouron	NNRTI
Retrovir	Zidovudine	AZT, ZDV	GlaxoSmithKline	NRTI
Reyataz	Atazanavir	ATV	Bristol-Myers Squibb	PI
Sustiva	Efavirenz	EFZ, EFV	Bristol-Myers Squibb	NNRTI
Trizivir	Abacavir+zidovudine+lamivudine	TZV	GlaxoSmithKline	NRTI
Videx	didanosine	DdI	Bristol-Myers Squibb	NRTI
Viracept	Nelfinavir	NFV	Pfizer/Agouron	PI
Viramune	Nevirapine	NVP	Roxanne	NNRTI
Viread	Tenofovir	TDF	Gilead	NRTI
Zerit	Stavudine	d4T	Bristol-Myers Squibb	NRTI
Ziagen	Abacavir	ABC	GlaxoSmithKline	NRTI