Antiretrovirals Pipeline Report

prepared for

Treatment Action Group

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The pipeline is bursting, with at least the following compounds twinkling in the eyes of scientists around the globe. It is by no means a full list, but those substances in red were presented at the recent CROI in Boston. There seems to be no lack of investigation — bench scientists are having a field day!

Compound	Class of Compound	Phase of Development	Pharmaceutical Co.
TAK 220	CCR5 antagonist	Preclinical	Takeda
PRO 140	CCR5 antagonist	Preclinical	Progenics
AK 602	CCR5 antagonist	Preclinical	Ono/Moravek
SCH D	CCR5 antagonist	"Early"	Schering Plough
BMS 806	entry inhibitor	Preclinical	Bristol-Myers Squibb
AMD-070	CXCR4 antagonist	Preclinical	Anormed
PA 457	budding inhibitor	Preclinical	Panacos
MV026048	NNRTI	Preclinical	Medivir
ACH-100,076	zinc finger inhibitor	Preclinical	Achillion
ACH-126,443 (Elvucitabine)	NRTI (reverses MT)	Phase IIb	Achillion
PRO 140	monoclonal antibody/CCR5 blocker	Preclinical	Progenics
SPD 756 (BCH-13520)	NRTI	Phase I	Shire Biochem
MIV-210 (FLG)	NRTI	Phase I	Medivir
D-D4FC (Reverset, DPC-817)	NRTI	Phase I	Pharmasset
DPC 961	NNRTI	Phase I	Bristol-Myers Squibb
L-870,810	integrase inhibitor	Phase I	Merck
T-1249	fusion inhibitor	Phase I	Trimeris/Roche
SCH C (SCH 351125)	CCR5 antagonist	Phase I/II	Schering Plough
UK-427,857	CCR5 antagonist	Phase I	Pfizer
Z-100	↑ MIP-1α production	Phase I	Zeria
TMC 114/r	protease inhibitor	Phase I/II	Tibotec
Peldesine	inhibits cellular factors	Phase I	Biocryst
Resveratrol	inhibits cellular factors	Phase I	Pharmascience
DEHSPM	inhibits hypusin/eIF-5A	Phase I	SunPharm
AXD455	inhibits eIF-5A	Phase I	Axxima Pharmaceuticals
BAY 50-4798		Phase I	Bayer
GEM 92		Phase I	Hybridon
TNX 355 (Hu5A8)	Anti-CD4 mab	Phase I	Tanox
Mycophenylate	inhibits cellular factors	Phase I/II	Hoffman-La Roche
PRO 542	attachment inhibitor	Phase II	Progenics
S1360/GSK810781	integrase inhibitor	Phase I/II	GSK/Shionogi Pharma
Cytolin		Phase I/II	Amerimmune Pharma
HGTV43	Anti-sense	Phase I/II	Enzo
Amdoxovir (DAPD)	NRTI	Phase II	Gilead
REV 123		Phase I/II	Novartis
AI-183 (DPC 083)	NNRTI	Phase II	Bristol-Myers Squibb

Calanolide A	NNRTI	Phase II	Advanced Life Sciences/Sarawak MediChem
TMC 125	NNRTI	Phase II	Tibotec
Alovudine (MIV-310, FLT)	NRTI	Phase II	Medivir (mitochondrial tox)
VX-175/GW433908 (fos-amprenavir)	protease inhibitor	Phase III	Vertex/GlaxoSmithKline
Tipranavir	protease inhibitor	Phase III	Boehringer Ingelheim
Capravirine	NRTI	Phase III	Agouron/Pfizer
Atazanavir	protease inhibitor	Phase III	Bristol-Myers Squibb
Emtricitabine (FTC)	NRTI	Phase III	Triangle Pharmaceuticals

Thanks to Ben Cheng for starting this chart a few years ago.

The following review is primarily from the 10th Retrovirus Conference in Boston. There is some earlier data from Barcelona XIV World AIDS Conference (July 2002) and data from the 4th Clinical Pharmacology meeting in Cannes (April 2003) as well. As organizing principle, I use the viral life cycle, i.e., where the drug acts, to organize this report.

Yellow brick or gold? Only time will tell

Many people are in need of new medications with different mechanisms of action and resistance profiles - an overwhelming body of evidence shows that even in people who maintain "undetectable" viral loads on successful therapy, the virus is able to continue to replicate and evolve (albeit at a slowed pace). The consequences are:

- evolution of drug resistance in some people, and
- persistence of HIV in some compartments in everyone.

Extracellular agents: attachment and entry inhibitors

With the exception of T-20 (Fuzeon, entfuvirtide), all FDA-approved anti-HIV drugs act inside HIV infected cells by interfering with reverse transcriptase (RT) or the HIV protease enzymes. The third major drug target that has been successfully exploited is HIV gp41—a molecule on the virus' surface that changes its shape in a specific way to allow viral "fusion" with the cell it is attacking and deliver its payload.

Why are investigators looking here, outside the cell? HIV drugs that work inside the cell can be efficiently neutralized by some cells, using primitive, innate self-defense mechanisms such as "efflux pumps" which sense toxins and eject them out of the cell. This kind of "cellular resistance" may be an important reason for viral persistence and evolution in people on seemingly potent combination therapies. "Extracellular ART" might circumvent this problem. More immediately, any drug working on a separate part of the virus' life cycle would have little or no potential for "cross-resistance" with the current drug regimens.

In a summary plenary lecture at this year's CROI, Eric Hunter from Alabama reviewed the progress of entry inhibitors and prospects for further development of extra-cellular ART. He emphasized the steps involved in HIV attachment and entry into cells, and explained how each of these steps might be targeted. The first step is HIV's gp120 molecule binding to a CD4 receptor and to a necessary "co-receptor" molecule on the cell surface (CXCR4 and CCR5 are the most common) for proper attachment.

Like a lock needing two separate keys, once both sites on gp120 are bound by CD4 and one of the co-receptors, gp120 flips back out of the way, exposing the virus' previously hidden harpoon molecule, gp41. gp41 is then free to pierce the cell and pull it in close enough to allow virus-cell fusion.

The first bull

T-20 (Fuzeon brand entfuvirtide)

The first inhibitor of gp41-mediated fusion, T-20, has proven active enough to receive approval for use in heavily antiretroviral-experienced people. The drug is administered by twice-daily subcutaneous injections. There were seven posters/talks on T-20 in Boston. Investigators presented 24-week pooled results of two T-20 studies— Toro 1, from North America and Brazil, and Toro 2, conducted in Europe and Australia.

Roche presented a summary of the pooled safety and efficacy data from these two Phase III studies (in which more than 600 highly pre-treated people received optimized therapy with or without T-20). The drug was effective at reducing HIV RNA levels by 10-100 fold in a slight majority of the T-20-treated group in both trials. However, up to 98% of people had injection site reactions to T-20 in these studies, with 20% reporting "moderate" or worse associated discomfort. Up to 3% of people at any time point needed pain medication to manage these problems. Another concern related to frequent injections is the possibility that bacteria could be introduced into the blood. There was a significant increase in the rate of bacterial pneumonia associated with T-20 in Toro 1 and 2 and a non-significant trend to more bacterial infections overall. Roche is looking into this. Another worry is the risk for allergic reactions to an injected protein: two cases of proven allergy to T-20 (and two more of suspected allergy) have been documented as of 1 April 2003, though many people (10% overall) developed elevated eosinophil counts, which might suggest an allergic reaction without additional symptoms.

In the Toro studies, 32.7% of treatment-experienced people receiving T-20 plus an optimized regimen of standard HIV drugs achieved undetectable levels of HIV in the blood (< 400 copies/mL) vs 15% of people who received a drug regimen without T-20. In both treatment arms, greater viral suppression was seen in people who had more active agents in their individualized regimen, were less treatment experienced and had less advanced disease. In Toro 1/2, T-20

reduced HIV-RNA levels to < 50 copies/mL in 20%/12% of people, compared to 7%/5% of those who took combination therapy alone. Results from Toro 2 were consistent with findings from Toro 1.

People in the T-20 arm experienced a mean CD4+ count increase of 65 cells/mm^3, compared to 38 cells/mm^3 in the control arm.

Problematic (painful and persistent) injection site reactions are the most common adverse event (AE) associated with T-20. As mentioned above, they occur in 98% of people who take the drug. Most are mild to moderate pain or discomfort, although 10% are severe and required prescribed pain relief. The combined safety analysis included patient exposures for longer than 24 weeks. While the overall incidence of bacterial infections was similar across both treatment arms when adjusted for time of exposure to the individualized regimen, bacterial pneumonia was observed at increased frequency in people in the T-20 arm (4.5% vs. 0.3%).

The other common AEs were headache (11.9%), insomnia (11.3%), and peripheral neuropathy (8.9%).

An preliminary analysis of 25 people in the Toro studies suggests there is no evidence of cross-reacting gp41 antibodies on the efficacy or safety of T-20 at 24 weeks.

Co-administration of T-20 with ritonavir, saquinavir/r, or rifampin did not produce any clinically relevant interaction.

As far as resistance goes, by week 24 of both Toros, 49.2% on T-20 met protocol-defined virological failure and they had on average a 21-fold loss of T-20 susceptibility, associated with changes in gp41 amino acids 36-45. Both *in vitro* and *in vivo* data indicate that HIV resistance to T-20 can and does occur. HIV variants with decreased sensitivity to T-20 contain mutations in the hr1 region of the gp41 complex. The most significant mutations are those located near the N-terminus of the hr1 region (the key T-20 binding area).

The Achilles' heel(s) of T-20 are thus various and sundry. From efficacy (16% of people go < 50) to the PISRs (in 98% of people) to the price (approx. $20,000/year wholesale!), T-20 is not a first-line drug. Given these factors, it is likely that the use of T-20 will be limited to very highly motivated people with few treatment options.

Joe Eron commented that to use these fusion inhibitors in combination may not be as easy as it seems. "… if TNX-355 prevents the conformational change in gp120, it might be antagonistic with T-20 rather than synergistic, because T-20 binds after the conformational change that exposes gp41. This could easily be tested *in vitro*. " As it must. (1 – 10)

More up-to-date information can be found at www.aidsinfonyc.org where you can find the Community Position Paper is regarding accelerated approval of T-20. Also, some post-approval negotiations with Roche and the HIV Community can be found at www.atac-usa.org.

T1249

T1249 is another injectable Roche peptide, similar in design to T-20 but binding to gp41 just downstream of T-20's binding site. It has been tested in phase I/II trials for activity against T-20-resistant viruses.

Animal studies have determined that the bioavailability of T-1249 averages 90% for the subcutaneous formulation. Doses ranging from 0.8 to 1.6 mg/kg yield plasma concentration in excess of 6 mg/ml, which is higher than the target concentration needed to maintain antiviral activity.

In abst 14Ib, T1249 was given to 23 people with both genotypic and phenotypic resistance to T-20 for 10 days. Reductions in viral load by day 11 were >10-fold for more than half (63%) of the people; there was one possible allergic reaction.

19/23 (79%) people had at least a 0.5 $\log_{10}$ drop in HIV RNA at day 11, which is in the range of non-significant. People failing T-20 for 24-48 weeks appeared to have better responses (7/7 people achieved >1 $\log_{10}$ decrease in HIV RNA; median day 11 decrease in HIV RNA –1.6 $\log_{10}$) than those who had been failing for >48 weeks (8/17 achieved >1 $\log_{10}$ decrease in HIV RNA; median day 11 decrease in HIV RNA –0.94 $\log_{10}$). (P)ISRs were not reported.

This was an interim analysis. The full data set from this study will hopefully be available for the IAS meeting in Paris. T-1249's development is roughly three years behind T-20.

There are no orally available fusion inhibitors in current development at Roche, so where we are is where we are likely to be for some time... (11, 12, 19)

CD4/Coreceptor antagonists

PRO 542

Progenics proposed Pro 542, a soluble CD4 receptor that binds to and neutralizes gp120 before binding can occur. The CD4 receptor region is

integrated into an immunoglobulin molecule to form a tetrameric protein synthesized using monoclonal antibody technology.

Results from phase I/II clinical trials of Pro 542 involving HIV+ adults and children were published in 2000. In the adult phase I study, volunteers were treated with a single intravenous infusion of Pro 542 at doses of 0.2-10 mg/kg (Jacobson, 2000). Pro 542 was well tolerated, and no dose-limiting toxicities were identified. AUC and serum concentrations of the pegylated agent increased linearly with dose, and a terminal serum half-life of three to four days was observed. Antibodies to Pro 542 were not identified. Transient HIV-RNA decreases were reported after single-dose administration.

In the phase I/II study enrolling 18 HIV+ children, Pro 542 was evaluated by single and multidose intravenous infusions (Shearer, 2000). The drug was well tolerated, and, as seen in the adults, dose proportionality was observed in terms of AUC and serum concentrations. Decreases of approximately 0.7 log copies/mL in plasma HIV-RNA levels were seen in four of six children treated with four weekly 10 mg/kg doses. After two weeks of treatment, three children had sustained reductions in serum HIV-RNA; the other children had rebounded to baseline levels.

A second set of phase II clinical trials, which are also being conducted in adults and children, were kicked off in 2000. These studies include people with HIV resistant to current antiretroviral options. The drug is currently being evaluated in an improved formulation for subcutaneous administration. (13, 19)

SCH-C & D

Scott Hammer discussed the orally bio-available CCR5 antagonist Schering C (SCH-C), developed by Schering-Plough. SCH-C is one of several small-molecule agents that have been studied as potential antagonists of CCR5. SCH-D, Schering-Plough's second CCR5 antagonist, has been shown to be even more potent than SCH-C *in vitro*.

SCH-C is an oxime-piperidine compound that, according to several *in vitro* evaluations, is a true antagonist of CCR5 receptor binding and signal transduction. *In vitro* observations also suggest that SCH-C is CCR5-exclusive—it has no effect on CXCR4-expressing cells—and has broad and potent antiviral activity against primary CCR5-tropic HIV isolates.

As for preliminary pharmacokinetics and safety data, one clinical trial enrolled 54 individuals to receive one of six single SCH-C doses: 25mg, 50mg, 100mg, 200mg, 400mg, and 600mg (Baroudy, 2002). Six volunteers in each group received the compound; three received placebo. The pharmacokinetics of SCH-C varied depended on the dose administered, but plasma levels were above the

IC90 for most of the doses employed. With many doses, twenty-four hours after administration, the drug's Cmin was still above the IC90, suggesting that once-daily dosing is possible.

However, there has been some concern regarding QT prolongation seen in individuals receiving the highest dose of SCH-C. The mean maximal increase in the QT interval, among individuals who received the 600 mg dose, was 60 msecs. There were no symptomatic events (e.g., arrhythmias), although more extensive follow-up testing was generally not conducted. These observations led the FDA to put the SCH-C development program on hold. However, the hold on development has since been lifted.

Three doses have been selected for further evaluation—25 mg, 50 mg, and 100 mg, all administered twice daily—and additional safety reviews will be conducted. One clinical trial had 12 people with SCH-C 25 mg BID and 12 people with SCH-C 50 mg BID (Baroudy, 2002). After ten days, the average reduction in HIV-RNA was approximately 0.7 log copies/mL in the 25 mg BID group and 1.1 log copies/mL in the 50 mg BID group. There were no discontinuations because of adverse events, the most common being headaches and altered taste. Some QT prolongation was observed—the mean increase was 11.5 msecs after ten days of treatment. (14, 19)

TNX-355

Preliminary data from TNX-355 (formally HU5A8) human trials was provided. This is a humanized IgG4 anti-CD4 domain that acts by binding to the CD4 receptor, and thus keeps HIV from entering after binding. It showed potent anti-HIV-1 activity *in vitro,* and studies in rhesus macaques and human peripheral blood lymphocytes indicated that it is not immunosuppressive. It is broadly inhibitory across all clades of HIV and inhibits both CCR5 and CXCR4 tropic virus. The antibody attaches to the side of the CD4 receptor in a way that does not interfere with its regular function as a chemokine receptor. Nor does it interfere with HIV's docking with the CD4 receptor, but it does block HIV from taking further steps in the process of entering the cell. Does it also then block the entrance of other normal agents? Based upon these preliminary data, a study was performed to determine the safety and preliminary anti-HIV activity of a single dose of TNX-355 in HIV+ people.

The study enrolled 5 sequential cohorts of 6 HIV+ people who received single IV doses of TNX-355 in an open-label dose-escalation study (see below). They had a mean baseline CD4 count of 354 cells/mm^3 and viral load of 5.1 log_{10} copies/mL. All were HAART-experienced and almost 2/3 of the people were on failing HAART at entry.

Dose	0.3	1	3	10	25 mg/kg
Viral load decrease	NR	-0.2	-0.68	1.48	-1.09 log_{10}
Time to nadir	NR	2	4	14	21 days

Duration of complete CD4 cell coating with TNX-355, ranged from 1–2 days at 1 mg/kg to 15–27 days at 25 mg/kg, which correlated with the day of viral load nadir. No significant adverse events were reported.

The single dose did not generate any natural antibody reaction. "Peak reduction in viral load occurred out to days 14 and 21," noted the presenter. The study team is in discussions with researchers who do kinetic modeling to try to understand the process.

The authors conclude, “Single doses of the entry inhibitor TNX-355 … acutely reduced viral load in HIV-1+ people. Further assessment of therapeutic potential awaits data from longer duration trials; a phase 1b multiple-dose study is planned.”

One advantage may be the possibility of administering TNX-355 on a schedule of once a week to once every three weeks. Macaques with multiple exposures to the monoclonal antibody developed antibodies to it that blocked activity of the drug. This issue, not seen in the single-dose human study, is one that will be closely monitored as the drug moves into phase II trials. (15, 19)

CCR-5 Inhibitors

TAK-220

TAK-220 is a CCR5 antagonist. The authors report that while the development of TAK-779 has been terminated due to local injection site reactions, TAK-220 appears to be a highly potent inhibitor of R5 HIV-1 replication and is orally bioavailable.

Data derived from studies using several CCR5-expressing cell lines and PBMCs showed that TAK-220 inhibited the binding of RANTES and MIP-1a to CCR5-expressing cells with an IC50 of 3.5 and 1.4 nmol/L, respectively, but did not inhibit the binding of MIP-1b even at a concentrations of 10 mumol/L.

TAK-220 appears to have a high specificity for the CCR5 receptor. It selectively inhibited HIV-1 infection mediated by CCR5 in PBMCs with mean EC50 and EC90 of 1.1 and 13 nmol/L, respectively, and this was unaffected by addition of high concentrations of human serum.

TAK-220 administered orally to fasted rats and monkeys at a dose of 5 mg/kg had a bioavailability of 9.5% and 28.9%, respectively, with the concentration in lymph fluid of rats about twice that in plasma. (16, 19)

AK602

AK602 is another CCR5 inhibitor. It has been looked at in mice and tested for anti-HIV activity.

It has shown activity against a wide spectrum of laboratory and primary R5-HIV isolates including multi-drug resistant HIV, and has shown potent inhibition of CCR5-gp120 binding. Previously reported CCR5 inhibitors (e.g., Sch-C, TAK779) fully blocked HIV infection as well as CC/CCR5 binding, while AK602, despite much greater anti-HIV activity, partially suppressed the interactions at the highest possible concentrations. The AK602 binding site on CCR5 was located near the 2nd extracellular loop. It remained on the cell surface for > 9 hours after washing, and blocked R5-HIV infection upon delayed HIV exposure. When administered twice daily to mice, it suppressed HIV replication and blocked CD42+ T-cell decrease. Preliminary pharmacokinetics showed favorable oral bioavailability in rodents.

AK602 may block the infectivity and replication of a wide spectrum of R5-HIV with partial inhibition of CC/CCR5 interactions. Because the long-term inhibition of CC/CCR5 interactions could lead to compromised inflammation/immune reaction, the present data warrant further development of AK602 as a potential HIV-specific CCR-inhibiting therapeutic for HIV infection. (17, 19)

UK-427,857

Data regarding another CCR5 inhibitor, UK-427,857, was presented by P Dorr. *In vitro* modeling indicates that UK-427,857 blocks viral replication at the point of membrane fusion by preventing the binding of the viral envelope gp120 to the co-receptor CCR5.

This small Pfizer molecule is already in phase I dose-ranging trials in humans.

Thus far, it appears that this compound has potency against isolates that utilize CCR5 for entry, with an IC90 < 10 nM; however, it has no activity against CXCR4-tropic viral isolates. UK-427,857 is non-competitive with regards to chemokine binding and does not induce intracellular signaling or trigger receptor internalisation. While it binds the receptor reversibly, it has a long binding half-life, which may lead to “advantageous” pharmacodynamics.

The authors conclude, “UK-427,857 is a prototype CCR5 antagonist for the treatment of HIV, with excellent potency against lab-adapted and primary strains. The predicted pharmacokinetic and safety profile of the candidate are such that the compound has the potential to block receptor binding when administered to humans with one or more *wt*-CCR5 alleles.” (18, 19)

The future is here

Very close attention is being paid to developments in the attachment inhibitor arena, in part because they have the theoretical potential to result in serious toxicities when used in infected people. CXCR4 and CCR5 are ubiquitous (everywhere) on cells of many different tissues and have a myriad of functions including normal cell growth and development processes. There is a concern that the sustained, long-term inhibition of CC/CCR5 interactions could produce significant adverse effects. The effects of interfering with the binding sites for these molecules in normal tissues are not known. An example of the hazards of CCR5 inhibition *in vivo* is SCH-C on hold due to its causing cardiac conduction abnormalities in early clinical trials. Another wild card for the use of co-receptor antagonists is the specter of the "co-receptor switch". Viruses can use either CXCR4 or CCR5 more efficiently. It has been commonly noted that many more "X4" viruses are present in people with late-stage AIDS, while people with very early infection nearly always have dominant "R5" virus populations. The possibility that inhibiting viral attachment to CCR5 would somehow cause a switch to CXCR4—which in turn might hasten people towards AIDS—is a concern. To date, most early clinical trials of CCR5 inhibitors have not shown R5/X4 switching to take place (at least over a very short time).

Whitcomb and colleagues presented a survey of co-receptor usage among people enrolled in the Toro trials evaluating the effect of T-20. They used a ViroLogic technique to try to detect mixtures of X4 and R5 viruses, rather than simply qualifying viruses as "all X4" or "all R5". This study demonstrated clearly that many (24%) people in the Toro trials (a very advanced, heavily pretreated population) had a mixture of R5 and X4 viruses, while 62% were predominantly R5 and a small minority was apparently exclusively X4. The sensitivity for detection of X4 variants is not that exquisite using the ViroLogic technique, so the proportion of people that really have mixtures of virus types may have been higher. In fact, all of the people having any X4s would likely be classified as "X4", or "SI" using traditional approaches (based on sequencing or MT-2 assay). In other words, these findings suggest that about half of people that would be candidates for therapy with new co-receptor inhibitors would have large proportions of circulating virus with preexisting resistance from the beginning (no "switch" required). In the case of X4 co-receptor antagonists, the efficacy and safety remain very unclear. (2, 20)

NRTIs

Viread – GS903, long-term efficacy

Gilead Study 903, conducted in the US, Europe and South America, has approximately 26% women. 96-week results presented at CROI show that Viread is maintaining efficacy in 82% of people (to < 400). CD4 cells have increased from 276 to 537. Discontinuation is approximately 15%. It is being compared to

d4T in a triple regimen (with 3TC + EFV). The metabolic analysis was out to only 48 weeks, and showed a significant favor for Viread with respect to limb fat loss. Those in the d4T arm experienced an HDL increase of 103 mg/dL vs an increase of 5 for Viread. As of February 2003, Viread was being taken by some 85,000 people in US, slightly less in Europe (it was approved later there). Viread is recommended to be taken with food. It's been seen that the major adverse events are renal impairment (kidney), nausea, rash and asthenia (weakness). (21) Prescription numbers in the US are reported by Gilead Sciences to be approximately 110,000 in mid-May 2003.

FTC (Coviracil, emtricitabine)

FTC is a thiacytidine nucleoside analogue. FTC is a once-daily nuke that may provide better adherence than BID. People who have already tried and failed lamivudine (3TC, Epivir) won't likely benefit from FTC, given that the M184V mutation confers high-level resistance to both drugs.

In FTC-301, a phase III, 48-week, double-blind, placebo-controlled (double dummy) trial that is being conducted in the United States, Europe and Latin America (Saag, 2002), antiretroviral-naive people with viral loads between 50,000 and 100,000 copies/mL are receiving Videx EC (ddI) and efavirenz (EFV) in combination with either FTC or d4T to measure viral failure, the frequency of genotypic mutations at time of failure and the CD4+ change from BL between treatment arms.

571 people have been enrolled into FTC-301. At baseline, the median viral load was 4.9log copies/mL and the median CD4+ count was 300 cells/mm^3. The proportion of people having VF through W48 was 5.3% in the FTC arm and 12.7% in the d4T arm ($p < 0.05$). The mean increase from baseline to week 48 in CD4+ was significantly greater in the FTC arm (153 cells/mm^3) than the d4T arm (120 cells) ($p < 0.05$). Also measured was efficacy failure—defined as virologic failure, death, progression to CDC class C, or loss to follow-up—which occurred in 13% of people in the d4T group and 7% of people in the FTC group. In terms of the proportion of people with undetectable viral loads, 87% in the FTC group and 79% in the d4T group had viral loads below 400 copies/mL. For < 50 copies/mL, 81% in the FTC group, compared to 70% in the d4T group, got there after 24 weeks of treatment.

Genotypic analysis was performed on 46 of the 49 confirmed VFs. Of the 33 genotypic evaluables failing d4T, 32 (97%) had mutations in the HIV polymerase gene as compared to 69% (9/13) from the FTC subgroup ($p < 0.05$). The M184V mutation was observed only in the FTC subset, 46% (6/13), while TAMs were observed in 8% (1/13) of the FTC arm and 21% (7/33) of the d4T group.

Although these results show that FTC was statistically superior to d4T, it is worth reminding that the combination ddI + d4T is not regularly recommended - side effects report, soon.

In a non-inferiority study, the French ANRS 099, people receiving a PI-based regimen with plasma HIV-RNA level < 400 copies/mL were randomized to continue their regimen (C) or to switch to once-daily combination (5 pills per day) of FTC, ddI, and efavirenz (QD). Intent-to-treat on available data (ITT) and intent-to-treat with missing = failure (M=F) analyses were conducted.

A total of 355 people were randomized; 86% were male with a median age of 41, a median duration of PI use of 35 months, and a median CD4 count of 540 cells/mm^3. At 540 CD4s, I ask myself why these people weren't offered a TI of some sort instead of rolled into another protocol of 48 weeks? The proportion (98%) of people with success at 48 wks is shown below.

Analysis	**C arm**	**QD arm**	**Difference C-OD**	**ULC**
ITT	92	94	-1.6	3.0
M=F	88	89	-1.8	3.8

[ITT, intention to treat; M=F, missing equals failure]

The ITT data was not given, but the OT data was seen to be statistically favorable to FTC for those < 50 at 48 weeks. Median CD4 count increase was similar between arms. Rates of treatment discontinuations were "low" (12.4% and 10.1%, no statistical difference). A significant increase in median fasting HDL cholesterol levels was observed in the OD arm as compared to the C arm. Other metabolic parameters remained similar between arms throughout the 48 weeks of the study. (abst 551, 333)

The same regimen was looked at in HIV+ children. PACTG 1021 is an ongoing phase I/II study in antiretroviral naïve or minimally treated children 3-21 yrs old. Study goals are to evaluate safety, preliminary efficacy, and pharmacokinetics of FTC/ddI/EFV in a pediatric population.

Thirty children (3-21 yrs) were stratified as either therapy naïve or < 6 wks of perinatal prophylaxis. At baseline, median age was 10.5 years, 57% were female, 2/3 were African-American. Median CD4 count and percentage at BL were 302 cells (16.5%). Median HIV RNA was 49,919 copies/ml. Initial doses were FTC 6 mg/kg; ddI 240 mg/m^2 and EFV adjusted for weight and age. PK studies at W2 determined whether plasma concentrations met protocol specified thresholds for each drug.

Three kids permanently discontinued therapy (one viral failure, one voluntary withdrawal, one grade 3 rash). There were two grade 3 or 4 laboratory

abnormalities that spontaneously resolved. Viral results (ITT, discontinuation = failure): at week 16 (N = 23), 87% < 400 copies/ml, 74% < 50 copies/ml. For CD4 at week 16 (N = 19), median increase is 220 cells (9%). FTC and ddI concentrations met threshold criterion, but EFV required a dose escalation. These preliminary results indicate virological activity for at least 16 weeks.

In another trial, experienced kids switched to FTC from 3TC. Naïve kids received FTC + d4T + lopinavir/r. Results are based on the W20 as-treated population for efficacy analyses and on all data collected for safety analyses. PK evaluation was conducted at steady-state.

In the naive group, median baseline VL and CD4 were 4.9 $\log_{10}$ and 715 cells/mm^3, respectively. In this group, at wk 20, the median changes in HIV-1 RNA and CD4 were -2.6 $\log_{10}$ and +213 cells/mm^3 (OT – only data available). Grade 3/4 lab abnormalities were reported in 17% (14/82) of the kids. Three (3) discontinued the study, 1 for SAE (anemia), 1 for virologic failure, and 1 withdrew consent. No experienced data was reported on.

N	51 naïve	31 experienced (4 yrs exp)
Weeks on treatment	19	32
Age	6 years	6 years

Although there appears to be a moderate increase in AUC with age, values are similar to those seen in adults (~10 hr*?g/mL). An FTC dose of 6 mg/kg QD in children of all age groups produces similar plasma levels to adults receiving 200 mg QD.

FTC-303 was a randomized, 48-week, open label equivalence trial in which people with HIV-1 RNA = 400 copies/mL either continued their 3TC regimen or switched 3TC 150 mg BID to FTC 200 mg QD. Those with plasma HIV-1 RNA = 400 copies/mL at week 48 were offered FTC as part of their HAART regimen in protocol FTC-350.

Out of 294 people, 227 (77%) randomized to FTC had HIV-1 RNA = 400 copies/mL at wk 48. Of these, 215 continued; 152 of 294 (51%) maintained suppression of HIV-1 RNA = 400 copies/mL and 139 (47%) = 50 copies/mL through wk 120 (2.3 yrs). Asymptomatic and transient elevations in CPK accounted for more than 2/3 of the overall Grade 4 adverse events.

FTC was submitted for approval in the fall of 2002. FDA announcement expected early July 2003. (22 – 26) The Community Position Paper will be on the internet at www.aidsinfonyc.org by 1 July 2003.

Amdoxovir (DAPD)

Amdoxovir (DAPD) is another NRTI developed by Triangle Pharmaceuticals and is now being guided through the development pipeline by Gilead Sciences. It is a dioxolane purine analogue with potent activity against HIV and HBV.

In vitro, amdoxovir has antiviral activity against AZT/3TC and d4T/3TC-resistant strains of HIV and is also active against strains harboring the Q151M or the 69SS substitutions, both associated with multiple-NRTI resistance. Also *in vitro*, two mutations arise: K65R and L74V.

As for amdoxovir's antiviral activity *in vivo*, preliminary results from an ongoing 96-week phase I study (DAPD-150) were reported at the 10th CROI (Thompson, 2002). Eighteen HIV+ people who had been treated with approximately 11 antiretrovirals over an eight-year period were randomized to receive either 300 mg or 500 mg amdoxovir on top of an optimized antiretroviral regimen. After 12 weeks, the median decrease from baseline in HIV-RNA was 1.53 log copies/mL in the 300 mg BID group and 0.75 log copies/mL in the 500 mg BID group.

As for safety, long-term toxicology studies indicated that high doses of amdoxovir were associated with lenticular opacities in monkeys and obstructive nephropathy in rats. Given these results, DAPD-150 was amended to require complete nephrologic and ophthalmologic assessments in all people. While no nephrologic toxicities were reported, 5/18 (28%) people discontinued the study because of lens opacity, although in these cases it did not end up having an impact on visual acuity. (27)

NNRTIs

Nevirapine - 2NN Study

The 2NN study compares nevirapine once daily, nevirapine twice daily, efavirenz, and the combination of nevirapine plus efavirenz. The results are at 48 weeks. Study participants also received d4T and 3TC. This is a study in 17 countries at 65 study centers sponsored by Boerhinger Ingelheim. Besides potency, factors in decision-making include resistance (not reported yet) and side effects (toxicities). 1216 treatment-naïve people were randomized to:

Drug	***Dose***	***Schedule***	***N***
Nevirapine (NVP)	400 mg	once daily (QD)	220
NVP	200 mg	twice daily (BID)	387
Efavirenz (EFV)	600 mg	QD	400
NVP+EFV	400/800 mg	QD	209

Inclusion criteria were any CD4 count, HIV viral load >5000, any stage of CDC-classification of HIV/AIDS. Failure at 48 weeks was the primary outcome. The

baseline characteristics of the people were relatively comparable in all study groups: 63% men, 34 yrs old, 190 CD4s, 4.7 log viral load (approximately 50,000 copies/ml), 21% CDC-class C, 5.3% had hepatitis B, and 9.5% had hepatitis C.

	Treatment success (VS)	***Virologic VS success***		
		>100,000	***<100,000***	
NVP qd	56.4%	65%	51.5%	71.1%
NVP bid	56.3%	63.6%	53.7%	68.2%
EFV	62%	67.8%	61%	71.1%
NVP+EFV	46.9%	61.7%	57.1%	

% <50 copies/ml (ITT):

NVP qd	70%
NVP bid	65.4%
EFV	70%
NVP+EFV	62.7%

Grade 3/4 clinical adverse events

	Hepatotoxicity	***Cutaneous Rash***	***CNS/Psychiatric***
NVP qd	1.4%	4.1%	1.4%
NVP bid	2.1%	3.1%	3.5%
EFV	0.3%	1.8%	5.5%
NVP+EFV	1.0%	3.8%	7.7%

Anxiety, depression, and insomnia/abnormal dreams:

	Total grade 3/4 events	***Discontinuations***
NVP qd	15%	24.1%
NVP bd	20.4%	1.2%
EFV	18%	15.5%
NVP+EFV	24.4%	29%

Elevated AST & ALT

NVP qd	13%
NVP bd	7.8%
EFV	4.5%
NVP+EFV	8.6%

Not significant - neutropenia, amylase, triglycerides, and alkaline phosphatase ranged in incidence from 0.5% to about 5% in the EFV and NVP groups.

2NN - Deaths

There were 25 deaths during the study, 2 of which were attributed to NVP: one woman from Argentina with toxic hepatitis without evidence of hepatic co-infection and one Steven's Johnson Syndrome in S Africa who died of MRSA septicaemia (sepsis) in hospital. One death was attributed to d4T use: lactic acidosis. 11 deaths were related to HIV and another 11 deaths were attributed to non-treatment and non-HIV related. None of the suicides were attributed to use of EFV. (28, 29)

Take me home!

The take home message from this trial seems to be that the double NNRTI idea is a bad one. Also, because NVP QD had more rash, many more discontinuations, more ALT and AST elevations, maybe its efficacy comes at too high a price. Although NVP BID looks almost as good as EFV in this study, the other two less successful arms may have served for nothing more than to diminish the clear comparison between NVP BID and EFV QD which was the original focus.

Capravirine

Capravirine (AG-1549) is an NNRTI that, according to Agouron/Pfizer, is active against single reverse transcriptase substitutions such as K103N, V106A, and L100I—three typical mutations to current agents. However, HIV with dual mutations at positions 100 and 103 resulted in a 24- to 40-fold decrease in sensitivity. A single Y181C mutation also decreased susceptibility to capravirine by 13-fold (Potts, 1999).

The clinical development of capravirine was dealt a setback in January 2001, when capravirine in animal toxicology studies demonstrated unexpected vasculitis in dogs. However, the capravirine dose associated with vasculitis was significantly higher than the dose currently being studied in humans and no cases of vasculitis have been detected in people participating in clinical trials. In December 2001, the FDA took capravirine off clinical hold, and studies have since resumed.

As for the potential effectiveness of capravirine, one phase I trial reported to date suggested that the drug is roughly ten times more potent than any of the current NNRTIs (Hernandez, 2001). Used as monotherapy, capravirine (2100 mg BID) resulted in an HIV-RNA reduction of 1.7 log copies/mL after ten days of treatment.

Preliminary results from a phase II clinical trial of capravirine involving 75 NNRTI-experienced people were presented two years ago at the 8th CROI in Chicago (Wolfe, 2001). The study compared two doses of capravirine—1400 mg BID and

2100 mg BID—to a placebo, with all three groups of people receiving nelfinavir and two new NRTIs. Approximately 25/50 (50%) evaluable people who received either dose of capravirine had HIV-RNA levels below 400 copies/mL after 12 weeks of treatment. Among the 12 people who had been receiving treatment for 16 weeks in the placebo group, HIV-RNA levels had decreased by 1.5 log copies/mL. Among the eight evaluable people in the 1400 mg group, the median HIV-RNA decrease after 16 weeks was 2.2 log copies/mL. As for the 10 evaluable people in the 2100 mg group, the median viral load decrease was 1.7 log copies/mL. In terms of adverse events, diarrhea, nausea, and vomiting occurred more frequently in the 2100 mg group than in the 1400 mg or placebo groups. At the time of presentation, four people had discontinued because of treatment failure and seven people had discontinued because of adverse events.

Nothing was presented in Boston, but Agouron has in fact dusted it off and is putting it back into development.

TMC 125

Tibotec's TMC125 is a flexible compound that, at least *in vitro*, has activity against both wild-type HIV strains and those containing single reverse transcriptase mutations, including L100I, K103N, Y181C, Y188L, and G190A/S—all of which are associated with resistance to current NNRTIs. In antiretroviral-naive people, seven days of TMC125 monotherapy resulted in a 1.99 log copies/mL reduction in HIV-RNA (Gruzdev, 2001). In fact, data presented at the 9th CROI suggested that the drug—as monotherapy—results in a similar initial rate of decline of HIV-RNA during the first week of treatment as a five-drug, PI- and NNRTI-containing regimen (Sankasing, 2002).

Although the data is very early, it is suggested that TMC 125 can change its shape in order to fit into various pockets of HIV. A new series of NNRTIs, including diaryltriazine (DATA) and dianilinopyrimidine (DAPY) compounds, is being developed. TMC125 is a DAPY compound. In a Phase I/II clinical trial reported in CROI 9, treatment-naïve people received 2 900 mg doses of TMC125 per day for one week. The mean viral load (RNA copies/ml) decreased 1.9 $\log_{10}$.

The poster says "Switching the conformations of NNRTIs from one mode of binding to another does not involve a significant energetic cost. A consequence of having several binding modes available is that a single drug molecule might be able to behave as a combination of drugs. NNRTI resistance mutations affect the size, shape, and/or chemical nature of the binding pocket; the NNRTIs could adopt different binding modes against different resistant RTs and thus remain effective." If this turns out to be the case, it may indeed be a novel approach, and not just a PR blurb. (30)

UC-781

UK's Biosyn suggests that another NNRTI, UC-781, can be formulated as a microbicide gel that is chemically and physically stable, providing potent and prolonged activity against HIV-1 without being toxic to target cells. A suspension gel formulation of UC-781 represents an interesting candidate for continued pre-clinical and clinical development. (31)

Novel benzophenone NNRTIs

Glaxo presented their medicinal chemistry program regarding the novel benzophenone NNRTI zone. They reported on three, and in the conclusions state that they "are potent new NNRTIs active against both wild-type virus and a broad-spectrum of NNRTI-associated mutant viruses including those known to be highly resistant to currently available NNRTIs. The mutations selected during passage with GW4511 are known to be associated with NNRTI resistance. These benzophenone compounds represent lead molecules for the discovery of a potent new generation NNRTI. (32)

Integrase Inhibitors

A novel class of integrase inhibitor compounds called pyranopyrimidines (PDPs) were noted to be potent in the test tube.

PDPs

The HIV integrase gene is essential for HIV replication and facilitates the integration of proviral HIV-DNA into the host cell genome. Unfortunately, it has not been easy to develop integrase inhibitors, despite the intense efforts of many investigators and many pharmaceutical companies. Challenges to development have included the lack of correlation of some integration inhibition assays with inhibition of whole virus replication, and non-selectivity, adverse pharmacokinetic properties, and toxicity of many of the candidate compounds described to date.

First there are the diketobutanoic ("diketo") acids, which work by sequestering the active divalent cation bound in the active site of the integrase gene. Once the gene has been inhibited, the HIV-DNA forms inactive, unstable circular structures, and the virus is unable to replicate.

S-1360

S-1360 is a diketo acid being developed by Shinogi Pharmaceuticals and GlaxoSmithKline. Preliminary data from early preclinical and clinical studies were reported at the 9th CROI and at the XIV International AIDS Conference in Barcelona. According to *in vitro* data reported at the 9th CROI, S-1360 is synergistic with all of the available antiretrovirals and has potency that is on a par

with lamivudine (Yoshinaga, 2002). In animal models, S-1360 was found to be 70% to 80% bioavailable and had a half-life ranging from one to two hours. As for clinical data from Barcelona, 18 HIV-negative study volunteers received single doses of S-1360 (Fujiwara, 2002). In all 18 people, the Cmax exceeded 4.75 mcg/mL and the plasma half-life ranged from 7.7 to 16 hours, meaning that once-daily dosing is possible. Phase I and II studies of S-1360, in HIV+ people, are under way.

L-870,812/810

There are also the napthyridine carboxamides, which include Merck's contenders L-870,812 and L-870,810 (Hazuda, 2002). These two compounds have potent antiretroviral activity in vitro—the IC95 for L-870,812 was 0.250 mM and the IC95 for L-870,810 was 0.110 mM, both in 50% human serum. L-870,812 has an oral bioavailability of 64%, and L-870,810 has an oral bioavailability of 49%, both in rhesus macaques.

L-870,812 has been tested in macaques infected with a recombinant SIV/HIV virus. SHIV-RNA was reduced by 1 to greater than 3 log in the treated laboratory animals and 4/6 macaques experienced an SHIV-RNA decrease to undetectable levels. Samples collected from the two macaques that did not achieve maximal SHIV-RNA suppression had evidence of an N155H mutation in the integrase gene.

Despite the structural differences between S-1360 and L-870810, a report at the 10th CROI noted a significant potential for cross-resistance between these two integrase inhibitors, which are both currently undergoing clinical development (Hazuda, 2003). A second report by the Rega Institute pushed for just the opposite, saying that the resistance profiles are in fact distinct. Wait and see … (33, 34)

Zinc Finger Inhibitors

Zinc finger inhibitors electrophilically attack the sulfur atoms in the cysteine residues, which leads to zinc ejection and incapacitation of the HIV nucleocapsid protein.

One such compound is ACH-0100703, currently being developed by Achillion Pharmaceuticals. It is a benzamide-disulfide that has demonstrated anti-HIV activity and reduced the cytopathic effects of both HIV-1 and HIV-2 without causing cellular toxicity. Achillion says that it is actively evaluating ACH-0100703 and related compounds as potential clinical candidates to move into clinical trials.

Not reported on in Boston.

Protease Inhibitors (PIs)

RO033-4649, just call me 4649

Roche reported on their medicinal chemistry program looking for a PI with activity against PI resistant viruses with optimal dose-exposure relationship (good drug levels with minimal dosing schedule and drug doses), and with no new side effects (lipid changes). This new PI was identified through structure-activity analysis focused on mutants with 1-5 PI resistance mutations and with phenotypic resistance of 2.5 to 10 fold or greater, for 1 or more PIs.

In vitro, 4649 was found to be active against wild-type HIV (strike up the band?), and appeared to have antiviral activity against PI resistant site-directed mutant viruses (lab strains) containing key PI mutations 84, 82, and 90. This drug has antiviral activity equivalent to that against wild type for all single and double site directed PI mutants and many multiple mutants. They looked at the activity against 50 "worse-case" PI clinical isolates using the Virologic Phenosense test. Many of these viruses had 10-50 and 50 fold resistance to current drugs. 62% of these viruses showed only a 0-10 fold shift in sensitivity to 4649. Many of the viruses with >50 fold resistance were not sensitive to it. 4649 may have promising activity against highly resistant PI clinical isolates. Phase I clinical evaluation has started. (35)

Atazanavir (ATV)

Bristol-Myers Squibb's atazanavir is a semi-symmetrical azapeptide agent with an IC50 of 2.6 to 5.3 nM. In dose-ranging studies involving HIV-negative volunteers, single doses of 100 mg up to 1,200 mg were explored (O'Mara, 1999). The drug was well absorbed and had a half-life ranging between 2.9 and 6.5 hours. Atazanavir doses of 400 mg or higher resulted in plasma concentrations above the necessary IC50 for more than 24 hours. A dose of 400 mg—two 200 mg tablets once a day with food—is being employed in phase III clinical trials.

In BMS study 034, eight hundred antiretroviral-naive people in North America, South America, Europe, Asia, and Africa were randomized to receive either of these drugs in combination with AZT and 3TC. At baseline, the median viral load was 4.9 log and the median CD4+ count was 282 cells/mm^3. More than a third of the study participants were women, and more than two-thirds were people of color.

After 48 weeks of treatment, the ITT analysis demonstrated that 70% of people in the atazanavir group and 64% of people in the efavirenz group had HIV-RNA levels below 400 copies/mL. It was determined that only 32% of people in the atazanavir group and 37% of people in the efavirenz group had HIV-RNA levels below 50 copies/mL. One explanation of these not great results may lie in the

approach to the intent-to-treat analysis. People were permitted to either reduce the dose of the NRTIs—or switch to another NNRTI (e.g., from zidovudine to stavudine)—in the event of toxicities. However, upon doing so, they were dubbed "failures" in the intent-to-treat analysis. What's more, if people had two HIV-RNA titers above 50 copies/mL in succession—even if their viral loads were below 50 copies/mL at the 48-week mark—they were also excluded from the ITT analysis. Unfortunately, an analysis excluding these two criteria has not yet been presented.

In the Boston presentation, in a study of more than 1,500 people treated in two phase II and three phase III studies, 26 resistant isolates were obtained—all of which harbored the I50L mutation. Other mutations associated with atazanavir resistance include A71V and K65R, neither of which is associated with resistance to other protease inhibitors, and G73S, which contributes to saquinavir, indinavir, and nelfinavir resistance (usually in the setting of the L90M mutation). Among people in clinical trials who received atazanavir and saquinavir, the I84V mutation has been documented, which is associated with broad cross-resistance to other protease inhibitors.

Results were reported on for lipid changes associated with people who were taking nelfinavir + d4T/3TC for 72 weeks and switched to atazanavir 400 mg once daily while continuing the NRTI backbone (study BMS 044, an ongoing, prospective, open-label, rollover/switch study). People on NFV were switched to ATV 400 mg; people on ATV were continued on either ATV 400 mg or ATV 600 mg. HIV RNA levels, CD4 cell counts, and safety (including lipid parameters) were assessed. A total of 346 people (37% female) were enrolled and treated; the median cumulative time on therapy was approximately 108 weeks.

Median Lipid Changes

After 96 weeks on ATV fasting LDL-C increased from about 100 mg/dl to 110 mg/dl. After 72 weeks on NFV LDL-C increased from 90 mg/dl to 132 mg/dl, but after switching from NFV to ATV LDL-C decreased to 99 mg/dl. HDL-C increased about 15% on both regimens (ATV or NFV).

Fasting triglycerides remained the same for people on ATV. For people initially on NFV, fasting TG increased from 93 mg/dl to 127 mg/dl, but after switching to ATV 400, went down to 102 mg/dl.

Total cholesterol increased in ATV from 166 mg/dl to 176 mg/dl. People initially on NFV saw TC go from 168 mg/dl to 202 mg/dl after 72 weeks, and 24 weeks after switching to ATV, TC was back to 169 mg/dl (-16%, P <.0001).

All people, whether on NFV or ATV, saw increases in HDL-C. The key difference is that LDL-C increased slightly on ATV over the 96 weeks but increased while

on NFV by about 40% and then decreased by about 25% in 24 weeks after switching to ATV.

About 10% of people on ATV reported lipodystrophy and there was no difference between the NLF and the ATV arms in respect to body shape changes. Jaundice was reported in 3% of people. For people who switched from NLF, 6% reported jaundice.

Total bilirubin was abnormal in 83% of people on ATV and 76% of people who switched from NFV to ATV.

	ATV 400 mg (n = 139)		***NFV ? Þ ATV (n = 63)***	
	044 Entry	***Week 24***	***044 Entry***	***Week 24***
< 400 c/mL (ITT)	-	111/139 (80%)	-	54/63 (86%)
< 50 c/mL (ITT)	-	80/139 (58%)	-	37/63 (59%)
		Median cells/mm^3		
CD4	472	556	543	584
		Median mg/dL [n]		
TC	180 (129)	176 (128)	202 (56)	169 (56)‡
Fasting LDL-C	110 (60)	105 (86)	132 (33)	99 (40)‡
Fasting TG	105 (103)	104 (110)	127 (47)	102 (52)‡

TC = total cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides
†As treated analysis, results maintained through 108 wks from start of AI424-008. ITT analysis for 008/044 selected cohort
‡p < 0.0001, NFV to ATV, mean % change, wk 24 vs entry

Discontinuations due to adverse events were comparable across cohorts (ATV 400 mg, 1%; ATV 600 mg, 2%; NFV to ATV, 3%), and no new safety issues were identified after approximately 108 wks of cumulative ATV treatment. Asymptomatic elevation in indirect bilirubin (without hepatic transaminase elevation) was the most frequent laboratory abnormality.

ATV Resistance

The resistance profile of resistant isolates was determined from people failing regimens containing ATV, showing the impact on susceptibility to ATV and other PIs. The phenotype and/or genotype of clinical isolates from people treated with ATV or ATV/SQV were determined. To confirm the role of mutations, individual and combinations of mutations were made in recombinant HIV proteases and viruses and their biochemical and phenotypic profiles evaluated.

Overall, phenotypic resistance to ATV was infrequent. Of the 19 isolates recovered from people experiencing virologic failure on regimens containing ATV as the sole PI (treatment duration 24-81 wks), all contained the unique protease substitution I50L. Eleven (58%) also contained an A71V substitution, 5 (26%) had G73S and 4 (21%) had K45R. The median fold change (FC) in ATV susceptibility among these isolates was 8.8 (range 3.5 to 36.6). Resistance was specific for ATV, since the susceptibility to all 6 marketed PIs increased and many had FCs of < 0.4. Those isolates that were resistant to multiple PIs upon treatment initiation exhibited increased susceptibility or resensitization coincident with the emergence of the I50L substitution. Thus, the I50L is the signature amino acid change observed following ATV treatment and results in ATV specific resistance and increased susceptibility to all other PIs.

In contrast, none of the 8 isolates obtained from the ATV/SQV dual PI regimen had the I50L substitution and nearly all isolates displayed a loss of susceptibility to other PIs in addition to ATV. ATV resistance in these people required the accumulation of several additional amino acid substitutions, including the I84V. Recombinant viruses containing I50L in a variety of backgrounds also displayed the phenotype of ATV-specific resistance and increased susceptibility to other PIs and were significantly growth impaired. Biochemical and structural studies are being carried out to understand the mechanism(s) involved.

PK in salvage

Combinations of active drugs are more effective in people who have experienced failure in multiple lines of antiretroviral therapy, provided that interactions do not alter exposure to the drugs. Tenofovir (TDF) and a Ritonavir-enhanced Atazanavir (ATV/r) regimen were combined as salvage therapy.

A prospective, open-label, multicentre trial in people with plasma HIV RNA > 10,000 copies/ml after at least 2 PIs and 1 NNRTI, where for the first 2 weeks, people were randomized to unchanged PI and NRTIs (group 1) or to a combination of ATV (300 mg once a day), RTV (100 mg once a day), and unchanged NRTIs (group 2). From wks 2–26, all people received ATV/r, TDF 300 mg (once a day) recycled NRTIs. 53 people were randomized. Samples for ATV and RTV PK were drawn at wk 2 and wk 6 in 11 people from group 2.

Ten males (mean 45 years) completed the PK part. At baseline, median CD4+ was 117 and HIV RNA was 5.1 $\log_{10}$ copies/mL. Median number of antiretrovirals taken prior to randomization was 11. ATV and RTV PK parameters were as follows:

	ATV			RTV		
	wk 2	wk 6	wk 6/wk 2	wk 2	wk 6	wk 6/wk 2
Cmax (ng/ml)	4,422	3190	0.72(0.50–1.05)	886	642	0.72(0.43–1.21)
Tmax (h)	3 (2–5)	5 (1–5)	-	3(2–8)	3(0-5)	-
AUC24 (ng.h/ml)	46,073	34,459	0.75(0.58–0.97)	7011	5217	0.75(0.44–1.24)
Cmin (ng/ml)	636	491	0.77(0.54–1.10)	43	39	0.91(0.73–1.13)
C24 (ng/ml)	696	513	0.74(0.53–1.02)	50	44	0.88(0.69–1.13)

At wk 2, ATV/r PK parameters are in line with data obtained in healthy volunteers. After TDF introduction, both ATV and RTV parameters were reduced. These findings suggest that decrease in ATV concentrations at wk 6 resulted from lowered RTV concentrations, even though the differences on most parameters did not reach statistical significance. The impact of TDF on ATV PK when given alone is –25% (see below). The mechanism of this interaction needs further investigation.

Another PK study was conducted to assess whether efavirenz (EFV), a metabolic enzyme inducer, had an effect on ATV exposure. In an open-label, randomized study, 34 non-HIV+ subjects received 400 mg ATV QD for 6 days. On day 7, they were randomly assigned to receive either 600 mg ATV QD or co-administered 300/100 ATV /r QD, each followed 2 hrs later by 600 mg EFV QD for 14 days. ATV /r was administered with a light meal. Co-administered 600 mg ATV/EFV and 300/100 ATV/r/EFV resulted in a 21% reduction and 39% rise in ATV AUC, respectively, vs 400 mg ATV alone.

A second study was conducted to assess whether ATV had an effect on either ethinyl estradiol (EE) or norethindrone (NE), a combination oral contraceptive (OC). It was an open label, non-randomized study, in which 22 healthy women stabilized on an OC regimen had PK profiles collected after the first 2 weeks of a complete OC cycle (day 1) and after the first 2 weeks of the next OC cycle (day 29) during which 400 mg ATV QD was co-administered from days 16 to 29.

Co-administration of daily doses of OC and 400 mg ATV produced 67% and 110% increases in Cmax and AUC of NE, respectively, and 15% and 48% increases in the Cmax and AUC of EE, respectively, compared to the administration of OC alone. No dose adjustment of OC is recommended, although it may be considered with a 110% rise! (36 – 40)

Again, there is a more complete update on ATV by TAG and the HIV Community at treatmentactiongroup.org. There is also a letter to the FDA regarding what is still missing and needed to be found out before this drug can comfortably be used by everyone with HIV.

GW 433908, fos-amprenavir

Discovered by Vertex Pharmaceuticals, the 908 compound (908) is the calcium phosphate ester prodrug of GSK's amprenavir (Agenerase). GSK has rights to 908 in the United States, Europe and some Asian countries, while Vertex has options to commercialize the drug in Japan and to co-promote it in the United States and Europe. Agenerase is an FDA/EMEA-approved protease inhibitor whose utility is somewhat limited by its standard daily pill burden of 16 capsules. The lower pill burden of 908 (two 700mg tablets twice daily) is an improvement in convenience. 908 can also be administered with low dose Norvir (ritonavir), which allows for lower dosing of 908 without loss of antiviral activity. The filing to the FDA was submitted in December 2002 for 908. It was not priority reviewed by the FDA. No final date set.

Researchers presented final 48-week results of the NEAT Study, a Phase III trial that evaluated the safety and efficacy of 908 vs nelfinavir in treatment-naïve people. In this multicenter trial, 249 treatment-naïve people were randomized to receive either 1,400 mg of 908 (2 tablets) twice daily or 1,250 mg nelfinavir (5 tablets) twice daily. Both patient groups used the drugs in combination with abacavir and 3TC in normal BID dosing.

The rate of GI side effects appears reduced with the new 908, although it was compared to NLF (famous for diarrhea, see below) and not directly to the old formulation. The viral load reductions were greater with 908 than with NLF. The lipid changes were comparable for the 2 drugs. There was more diarrhea of at least moderate severity reported for people taking NFV (18% vs 5%).

People were treatment naïve. The study was conducted in the USA, Panama, Puerto Rico, and South Africa. The patient group in this study varied greatly in CD4 count and viral load. 45% had >100,000 copies/ml viral load, and 18% had <50 copies/ml. 20% had CDC class C. 31% of participants were women.

At week 48, 66% taking 908 had <400 copies/ml vs 51% taking nelfinavir (ITT R/D=F, rebound or discontinuation = failure). 908 performed better as well when evaluated for <50 copies/ml of viral load, (55% in 908 vs 41% with NFV).

Why did 908 perform better in this study than nelfinavir? The study results showed that failures due to adverse events & other non-virologic reasons were comparable between the NFV and the 908 groups. But there were fewer virologic failures for people taking 908: 14% in the 908 group vs 28% in the NFV group. 4% of people prematurely discontinued from the study due to insufficient viral load response in the 908 group vs 13% in the NFV group. Looking at response by people of non-virologic failures the results were relatively comparable. For people with >100,000 copies/ml, 55% taking 908 went <50 copies/ml vs 24% taking NFV (ITT RD=F). CD4 increases were about the same in each group: 201 vs 216.

There was more hypersensitivity (ABC, one imagines) in the 908 group (9% vs 5%) and more rash (ABC again?) in the 908 group (7% vs 2%). Why was there more presumably ABC rash/hypersensitivity reactions in the 908 arm? For the remaining clinical adverse events the profiles were comparable between the 2 drugs (nausea 4-5%, vomiting 2-4%, fatigue 1-2%, headache 2%, insomnia 1-2%, weakness 1-2%). Liver elevations and cholesterol counts were similar in both arms. The NFV group's triglycerides levels were > 200 mg/dL. Also, the drop out rate was very high: 30% (908) was the good arm, vs 46% (NFV).

The Context Study was a 24-week efficacy and safety look at 908/r vs Kaletra in PI-experienced people. The 24-week study results show Kaletra performed better virologically. People had prior experience with at least 1 or 2 protease inhibitors. People could be NNRTI naïve or experienced. There was no CD4 criteria. This was a non-inferiority analysis, that is, they had to show that the 908 results were not inferior to Kaletra. The study took place in Europe, US, Chile, Puerto Rico, Canada, and Australia. The people in this study also were a fairly advanced group in terms of HIV progression. 34% had CDC class C. CD4 counts ranged between 234 and 290. Tenofovir was available for people in this study and it was part of about 11-13% of regimens in all 3 arms.

People were only permitted to enter this study if resistance testing verified that there were at least two nucleoside reverse transcriptase inhibitors that retained sufficient activity. The interpretation of the genotype was done via “Guideline Rules” from Visible Genetics. These rules were updated 3 times during the course of the study as new information became available.

Viral load reduction over the 24 week study, as evaluated by the mean time-averaged change from baseline, was: -1.48 log in the 908 qd group, -1.50 log in the 908 bid group, and –1.66 in the Kaletra group.

Virologic Success (ITT R/D=F)

% <400 copies		**% <50 copies**	
58%	908/r qd	40%	908/r qd
60%	908/r bid	42%	908/r bid
69%	Kaletra	48%	Kaletra

The presenter did not know how to answer the question of why the actual viral load was not reported. In other words, the final drop could have been a whole log lower for some people, and could have differentiated the two treatments even more. If the actual viral drop and not the <50 had been reported, maybe in fact, non-inferiority would not have been achieved. In other words, did GSK use AAUCMB in order to compare to Kaletra and not lose? AAUCMB is a technique recognized by the FDA used in studies where a majority of people are not expected to achieve complete viral suppression (BLD). In at least 2 of the 3

arms, there should not have been any reason to not expect reaching BLD (viral load averaged 14,000 copies, Kaletra can do that with one eye shut, 908/r BID has been previously shown to also effectively do that).

	908/r QD	908/r BID	LPV BID
Virologic failure	34%	27%	21%
VRNA rebound	13%	11%	11%
VL suppression	22%	17%	11%
Non-virologic failures	8%	10%	9%
Adverse events	<1%	<1%	6%
Lost to follow-up	4%	7%	2%
Consent withdrawn	2%	0%	<1%

Drug Related Adverse Events of At Least Moderate Severity

	908/r qd	908r bd	LPV/r
Any grade 2-4	19%	35%	34%

Lab Abnormalities (grade 3-4) seemed equal across arms. There were more serum lipase elevations in the LPV arm vs the 908 arms.

543 people were screened and 320 were randomized. The 223 people screened but not randomized, presumably lacked active NRTIs. The study population is thus a pretty selective one since it represents only the proportion of PI-experienced people who are more likely to achieve treatment success with a new regimen, given that they are receiving at least 3 active agents with the new regimen. And they were not expected to go BLD? Use of NNRTIs was not allowed. At this point, why not?

While the results of this data were interpreted as indicating the non-inferiority of the two 908 regimens to KAL, some questions were raised. First, the KAL arm appeared to have superior efficacy.

Secondly, Joe Eron inquired from the audience regarding the appropriateness of AAUCMB as an indicator of efficacy. His point was that using an average area under the curve minus baseline AAUCMB probably underestimates the efficacy of therapy in people who achieve suppression <50 copies, especially if they start from a relatively low viral load at treatment initiation.

While everyone did relatively well in this study, the patient screening criteria was a likely important issue in the success rates observed. This study shows that 908 is a potentially useful agent for second or third line PI therapy, but more data is needed.

Poster 598 suggests that 908 virologic failures are still susceptible to the gamut of PIs (no cross-resistance). Experience tells us that no matter how good the *in vitro* data, real life can't be beat. Less than 10% of PI users use 908, so we do not know what they switch to and how well it works if they are one of the ~30% of people in whom it fails. (41 – 45)

Tipranavir (TPV)

Tipranavir (TPV), the first non-peptidic protease inhibitor (PI), demonstrates viral load responses against multiple PI-resistant HIV-1 in clinical studies. Being non-peptidic, in theory, it will bind more flexibly to the active site of the HIV protease. TPV induces the cytochrome P450 pathway, whereas current protease inhibitors either inhibit or both inhibit and induce this enzyme system, so in order to reverse the rapid metabolism of the drug by the P450 and to allow dosing with food, it must be dosed with RTV.

BI 1182.52 was designed to determine the optimal dose for use in Phase III trials. It is a multicenter, international, randomized, blinded trial of 3 doses of TPV/r (500 mg/100 mg; 500 mg/200 mg; and 750 mg/200 mg). Entry criteria included experience of all 3 available classes of antiretroviral, including at least 2 PIs and at least one primary PI mutation. Any CD4+ cell count was allowed, and any viral load > 1000 copies/mL. Background therapy was optimized after 2 weeks of functional monotherapy with TPV/r. The primary endpoints were viral load reduction at 2 wks and specific adverse events (AEs) at 4 wks. Although I say functional monotherapy, because the Cmin aimed for is 10 times the protein adjusted IC90, most everyone, even at the low (and ultimately discarded) dose, had their IC90 covered by their dose of TPV. Trough concentrations were 21-22 nM for the 500/100, the aim being 20. The chosen dose, 500/200, reached a trough concentration of 29-32 nM.

A total of 216 people were randomized. All people were triple class experienced, with at least 2 failed PIs in their chart history, and at least one primary PI mutation. Prior use of individual PIs ranged from 37.5% for lopinavir to 79.6% for indinavir. The median baseline viral load was 4.5 log copies/mL and CD4+ cell count was 153 cells/mm^3. After 2 wks, the median change in viral load was -0.9 log, -1.0 log, and -1.2 log in the three arms (intent-to-treat; last observation carried forward); these values did not show a statistically significantly difference. Overall, 15.3% of people experienced = Grade 2 diarrhea and 11.6% experienced vomiting. A dose-dependent trend was observed for Grade 3/4 AEs, laboratory abnormalities, and AE related treatment discontinuations. Eleven people (5.1%) experienced serious AEs of any causality during the first 4 wks.

The most common adverse events associated with tipranavir were diarrhea, nausea, fatigue, headache and vomiting. In addition, the elevation of transaminases has been observed in people treated with tipranavir.

	Viral Load (ITT:LOCF) Reduction at day 14	Reduction at day 28
500/100	0.87 log	1.17 log
500/200	0.97 log	1.27 log
750/200	1.18 log	1.48 log

Impact of Prior PI Resistance

All people had at least 5 PI mutations. People were classified by whether they had 6-10 mutations, 11-15 mutations, 15-20 mutations, or greater than 20 mutations. The amount of PI resistance did not appear to effect response to TPV. Regardless of how many mutations people had, on average the reductions in viral load from baseline were at least 0.8 log and ranged to as high as 1.2 log, but only in the 500/200 and 750/200 dose groups. People with more than 20 mutations in the 500/100 group dropped viral load by only 0.2 log.

At the Lisbon ECCAT and since published, TPV was shown to have a singular resistance pathway that is now showing to be true *in vivo*. Study spokesperson Gathe identified a group of 4 protease inhibitor mutations (L33I/V/F, V82A/F/L/T, I84V, and L90M) and named them Universal PI-associated mutations (UPAM). Using phenotypic resistance testing he reported that if people had none of these UPAMS they had virtually full sensitivity to all protease inhibitors including TPV. If people had 1 or more of these mutations phenotypic resistance ranged from 5 to 40 fold to the currently available protease inhibitors. But the fold change in susceptibility remained 2.2 or less to tipranavir regardless if people had 0 or 3 of these mutations. This interesting concept needs to be confirmed independently in order to verify that this simplified way of measuring resistance mutations is significant and true.

Reductions in viral load by TPV were comparable regardless if people had 0, 1, or 2 of these UPAMs, but viral load reduction was compromised if 3 UPAMS were present:

Impact of UPAMS on viral load response at day 14

# of mutations	**500/200 median**	**750/200 n**	**median n**	
0	0	n.a.	9	-1.19
1	23	-1.15	72	-1.25
2	24	-1.40	79	-1.24
3	21	-0.33	50	-0.54

Severe (grade 3/4) Adverse Events to Day 28

	500/200	**750/200**
N	72	71
Any AE	12.5%	16.9%
Diarrhea	4.2%	5.6%
Triglycer.	1.4%	1.4%
ALT/AST	1.4%	1.4%
Headache	2.8%	0
Rash	0	2.8%

Grade 3/4 Lab Abnormalities to Day 28

	500/200	**750/200**
Liver Function		
ALT	9.9%	12.7%
AST	1.4%	2.8%
Lipids		
Triglyc.	15.5%	11.3%
Chol.	0	2.8%

At day 56, virologic efficacy appeared sustained (viral reductions maintained at 1 – 1.2 logs below baseline).

Adverse Event-related Study Discontinuations

	500/200	**750/200**
< 4 weeks	4.2%	7.0%
< 24 weeks	5.6%	15.5%

In the same study, a PF analysis was done of all people to choose the final dose. The preliminary target median plasma concentration for TPV was set at 10X the protein adjusted IC90 in multiple PI resistant HIV-1.

The median trough plasma concentrations of TPV exceeded the target value in all arms.

TPV/r plasma concentrations	**Day 7**	**Day 14**
500/100	21.8 ?M	20.1 ?M
500/200	32.1 ?M	29.11?M
750/200	52.2?M	42.6?M

78% and 77% of people in the 500/200 and 750/200 arms, achieved the target plasma concentration, as compared with 48% in the 500/100 arm. There was greater variability of plasma levels in the 750/200 arm.

The consistency of plasma trough levels from days 7 to 14 indicate that steady state is reached within the first 7 days of treatment in these treatment experienced people (switched from PI). These results indicate that a consistent viral load response was achieved in people achieving trough plasma concentrations > 15 ?M; more people in the 500/200 and 750/200 arms of the study achieved this concentration than in the 500/100 arm.

In another substudy, the phenotypic susceptibility to TPV was measured in multiple PI experienced people. Phenotypic analysis was conducted using the Virco Antivirogram assay. Baseline phenotypic susceptibility to TPV was maintained in the majority of isolates that were resistant to available PIs. There was an apparent breakpoint in TPV susceptibility at an IC50 approximately 2-fold WT; this point required the accumulation of a large number of protease gene mutations. (46 – 49)

TMC114

Tibotec calls TMC114 a "resistant-repellant" compound. More specifically, TMC114 has been designed not only to bind with high affinity to typical active sites of the protease enzyme, but also to remain active because of its unique flexibility in the event of mutations that arise during therapy with other protease inhibitors. The presenters described the compound as "a unique structure with a double ring and a tight binding at the active site."

Localized oral and peripheral paresthesias have been observed in 3/6 (50%) volunteers receiving the 3200 mg TMC114 dose.

In a phase IIa clinical trial reported at the 10th CROI, 50 people with a protease inhibitor-failing regimen—and a history of other protease inhibitor failures—were randomized to switch their current protease inhibitor for one of three doses of TMC114 (combined with 100 mg ritonavir) or to continue their failing regimen (Arasteh, 2003, Epimed Clinic, Berlin). At baseline, people had a median viral load of 4.3 log copies/mL and 46% were resistant to all of the currently available protease inhibitors. After 14 days, the people who did not switch their protease inhibitor(s) for TMC114 experienced a slight increase in their viral loads. Those in the 300 mg, 600 mg, and 900 mg TMC114 groups had median HIV-RNA decreases of 1.24 log, 1.5 log and 1.23 copies/mL, respectively (median: -1.35 logs). Not surprisingly, no one in the control group achieved undetectable viral load levels (<400 copies/mL); after 14 days of treatment, 46%, 42% and 31% of those in the 300 mg, 600 mg, and 900 mg TMC114 groups achieved viral loads <400 copies/mL. Importantly, there was no correlation between baseline resistance and virologic outcome.

About a third of the people experienced lower gastrointestinal (GI) tract problems such as diarrhea and flatulence; headache (16%) and dizziness (11%) were also observed. One patient discontinued due to GI events and another due to hepatotoxicity. Overall, two people in the 300 mg twice daily group, 2 people in the 600 mg twice daily group, and 1 patient in the 900 mg once daily group had grade 3/4 ALT, AST, or GGT elevations. One patient in the control group had a grade 3 AST. Arasteh said they are following these people after stopping the trial drug and switching to a new salvage regimen, but that analysis is not yet available. When an audience member expressed concern that this was yet another PI that used low-dose ritonavir. Arasteh said they "don't know yet if it is necessary to boost this compound, there are other ongoing trials" that do not use ritonavir as a boost.

One poster showed the discovery process, looking for a PI that would work against resistance seen in the field now and would not allow development of future resistances!

A second poster is a safety study in non-HIV+ people. They were still using the liquid formulation, which they have finally gotten rid of. They now have (as of 28 March '03) switched everyone to capsules. The GI effects (78% diarrhea) were due to this pegylated formulation. RIT helped the safety/tolerability of TMC alone – not a good sign! (50 – 53)

Maturation inhibitors (they think)

PA-457

PA-457 inhibits HIV-1 replication by interfering with a late step in the virus lifecycle. It is orally bio-available in rats with a half-life of 2-3 hrs. PA-457's potential was examined by analyzing 1) in vitro activity against drug-resistant isolates (to NRTIs, NNRTIs, and PIs); 2) mechanism of action (late events in the viral life cycle– the protease function and the viral protein processing); and 3) synergy with approved drugs (*in vitro*).

PA-457 retains low nM IC50 against all drug-resistant HIV-1 isolates tested. The compound is strongly synergistic with AZT, nevirapine, and indinavir in the test tube. PA-457 inhibits replication late in the virus life cycle, but does not target viral protease. It causes a defect in *gag* processing. Specifically, p25 to p24 processing is inhibited, a phenotype that is strongly associated with inhibitors of virus budding/maturation.

PA-457 potently inhibits replication of HIV-1 isolates resistant to all classes of currently approved drugs (including highly NNRTI-resistant viruses containing Y181C and K103N/Y181C mutations and PI-resistant viruses containing V82A, I184V, and V82A/I184V mutations). Studies are underway to identify the specific

molecular target for this inhibitor. Further development of PA-457 as an antiretroviral drug candidate will continue. (54)

Like much else of what was on display in Boston, PA-457 needs a lot of work and investigation just to find out what it is and how it works (if it really works!), but it shows that there is a lot of basic molecule investigation and much to look forward to in the next few years.

Are there more drugs coming down the pipeline? That deserves a wholehearted affirmative. There may be jams along the way for many, maybe the majority, of these drugs, but as quickly as any of these drugs loses favor (or efficacy or safety), there will be new ones (maybe from new classes) coming along. Social and support services may not continue here in the US, for both HIV+ people or to keep those non-positives, well, non-positive, but drugs will be there. Of course, these therapies are not getting cheaper, and at what cost is this pipeline so full?

References available online (http://treatmentactiongroup.org/tx/pipelineRef.html).