

View from the Pipeline: The 2004 Review of Experimental Antiretrovirals

Joseph J. Eron, Jr., MD
Associate Professor of Medicine
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

SUMMARY BY TIM HORN
EDITED BY ROY M. GULICK, MD, MPH

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THERE ARE 26 MEDICATIONS APPROVED FOR THE TREATMENT OF HIV infection. This latest tally includes 19 unique antiretroviral agents, three prodrug/extended-release formulations of older drugs, and four fixed-dose combinations (including the most recent arrivals: Gilead's Truvada and GlaxoSmithKline's Epzicom [see PRN Capsules on page 2]). Despite these impressive numbers, there is an indisputable need for new anti-HIV compounds that have potent and durable efficacy profiles, unique resistance patterns, patient-friendly dosing schedules, and minimal toxicities. What follows is an overview of some of the newest antiretroviral contenders, including some of the more recently approved agents and a number of the experimental agents in various stages of development.

I. Nucleoside/Nucleotide Analogues

Emtricitabine (Coviracil)

EMTRICITABINE (COVIRACIL), FORMERLY KNOWN AS FTC, IS A THIACYTIDINE nucleoside analogue that was originally developed by Triangle Pharmaceuticals and is now in the hands of Gilead Sciences. It was approved in July 2003 and is prescribed at a dose of 200 mg once daily.

Although emtricitabine is a unique antiretroviral, its comparison to lamivudine (Epivir) is fitting. HIV resistance to emtricitabine is via the same mechanism as resistance to lamivudine: the M184V mutation confers high-level resistance to both drugs. However, as Dr. Eron pointed out, it appears the emtricitabine is more potent than lamivudine, at least over the short term, and has a longer plasma and intracellular half-life than lamivudine. "It's still not clear if this will translate into a lower likelihood of developing resistance," he said. "This might be the case, but there haven't yet been any studies, directly comparing emtricitabine and lamivudine in previously untreated patients, to determine this." There have also been questions as to whether emtricitabine is as well tolerated as lamivudine.

In early August, Gilead received the green light from the FDA to begin marketing Truvada, a fixed-dose combination (FDC) tablet containing 300 mg tenofovir (Viread) and 200 mg emtricitabine.

Once-Daily Abacavir: Fixed-Dose Abacavir and Lamivudine (Epzicom)

UP UNTIL RECENTLY, ABACAVIR (ZIAGEN) WAS PRIMARILY STUDIED IN combination with zidovudine (Retrovir) and lamivudine, in an effort to bolster the appeal of an all-NRTI regimen consisting only of Trizivir. Because of lackluster clinical trial results comparing Trizivir and other all-NRTI regimens to more orthodox combinations drawing upon two classes of antiretrovirals, more recent studies have attempted to define the utility of abacavir in combination with one other NRTI—usually lamivudine—and either a PI or NNRTI.

No stranger to the FDC market, GlaxoSmithKline has received FDA clearance to begin marketing Epzicom, a once-daily tablet containing 600 mg abacavir and 300 mg lamivudine.

Pharmacokinetics data supporting once-daily use of abacavir has been presented (Piliero, 2003), as have clinical trial data comparing once- and twice-daily abacavir. CNA30021 randomized 770 antiretroviral-naive patients to receive either once-daily (600 mg QD) or twice-daily (300 mg BID) abacavir in combination with once-daily doses of lamivudine and efavirenz (Sustiva) (Gazzard, 2003). The median viral load at baseline was 4.89 log₁₀ copies/mL and the median CD4+ cell count was 262 cells/mm³. Approximately 44% of the patients in the study had HIV-RNA levels in excess of 100,000 copies/mL.

After 48 weeks of treatment, 66% of patients who received once-daily abacavir had undetectable viral loads (<50 copies/mL), compared to 68% of those given the drug twice daily. The median increase in CD4+ cells after 48 weeks was also comparable, with patients in the once-daily abacavir group experiencing an increase of 188 cells/mm³, compared with an increase of 200 cells/mm³ among patients in the twice-daily abacavir group. The differences between the two groups were not statistically significant.

Toxicity rates were also similar in the two treatment groups. Approximately 9% of patients in the once-daily group experienced a hypersensitivity reaction, compared to 7% in the twice-daily group. Of note, hypersensitivity reactions occurred more frequently in this study than were noted in some earlier studies (~5%).

Additional 48-week data from a phase III clinical trial (CNA30024) demonstrated that a regimen consisting of abacavir (twice-daily), lamivudine and efavirenz is non-inferior to a regimen consisting of zidovudine (Retrovir), lamivudine, and efavirenz (DeJesus, 2003). Of note, CD4+ cell count responses were greater in the abacavir-treated group when either the changes in the absolute CD4+ cell counts or the CD4 percentages were compared (see Figure 1).

"A fixed-dose combination involving abacavir and lamivudine is appropriate for treatment-naive patients, provided that they are given a highly potent third agent, such as efavirenz or boosted atazanavir, lopinavir, or fosamprenavir," Dr. Eron said. "We know that we shouldn't give a triple-NRTI regimen consisting of abacavir, lamivudine, and tenofovir or didanosine. We've seen the data concluding that these combinations have a high risk of treatment failure. Fixed-dose combinations are good options for our antiretroviral-naive patients, but it's still not clear what role they'll play for our antiretroviral-experienced patients. In general, most of my treatment-experienced patients are taking drugs twice a day. And in this setting, I would probably give abacavir twice a day."

D-D4FC (Reverset)

NOW IN PHASE II CLINICAL TRIALS IS D-D4FC (REVERSESET), A CYTIDINE analogue being developed by Pharmasset Pharmaceuticals and Incyte Corporation. Reverset's chemical name is D-D4FC and was formerly

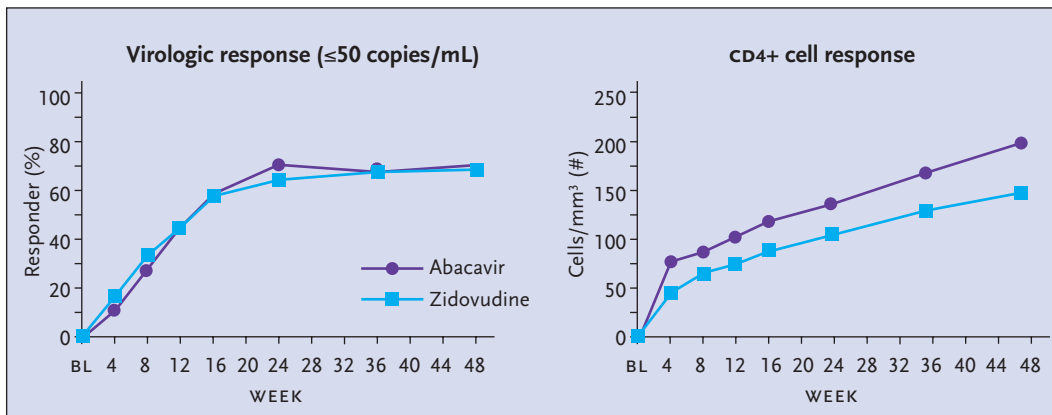


FIGURE 1. CNA30024: Abacavir (+ Lamivudine/Efavirenz) vs Zidovudine (+ Lamivudine/Efavirenz)

Source: DeJesus, 2003

known as DPC-817 when it was being developed by DuPont Pharmaceuticals and Bristol-Myers Squibb.

In vitro resistance data have been encouraging. According to a study published in 2003, D-D4FC was highly effective in inhibiting subsets of lamivudine- and zidovudine-resistant HIV variants—including those containing L74V, M184V, and various TAMs—but was less potent against variants harboring multiple-NRTI-resistant mutations, most notably Q151M (Geleziunas, 2003). *In vitro*, D-D4FC selects for the K65R mutation, conferring 5.3- to 8.7-fold resistance to the drug (and multiple-NRTI resistance).

Results of a Phase Ib/IIa study presented by Dr. Robert Murphy of Northwestern University and his colleagues were presented at the xv International AIDS Conference in Bangkok (Murphy, 2004). The placebo-controlled study (Study 202) involved 30 treatment-naïve and 10 treatment-experienced patients. The treatment-naïve patients received 50 mg, 100 mg, or 200 mg D-D4FC monotherapy for ten days. Eight treatment-experienced patients, none of whom were maintaining undetectable HIV-RNA levels while taking standard regimens, added 200 mg D-D4FC to their therapies for ten days (two added D-D4FC placebos).

The mean reduction in viral load among the treatment-naïve patients in the three treatment groups ranged from 1.67 log₁₀ copies/mL to 1.77 log₁₀ copies/mL. Among the treatment-experienced patients, the mean reduction in viral load was 0.8 log₁₀ copies/mL. What's more, seven of eight treatment-naïve patients (in the 200 mg D-D4FC group) and four of eight treatment-experienced patients achieved undetectable viral loads (<400 copies/mL) following ten days of therapy. The drug was well tolerated. By report, no new resistance mutations developed during the ten days of therapy.

A Phase IIb clinical trial (Study 203) involving 180 treatment-experienced patients began enrollment in June. Depending on the results of this study, a Phase III clinical trial will be initiated by mid 2005.

SPD754

ANOTHER CYTIDINE ANALOGUE IN DEVELOPMENT IS SHIRE PHARMACEUTICALS' SPD754. The drug was originally developed by BioChem Pharma, under the chemical names BCH-10652 and (-)-dotc. Pharmacokinetics data indicate that SPD754 is appropriate for once-daily administration.

Preliminary safety and efficacy data are available. A ten-day placebo-controlled study involving 63 antiretroviral-naïve patients was reported at the 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment, held in Paris in July 2003 (Cahn, 2003). The once-daily doses

ranged from 400 mg to 1600 mg. After ten days of therapy, reductions in HIV-RNA ranged from 1.18 to 1.65 log₁₀ copies/mL. No adverse events were reported.

Of potential concern is the interaction between SPD754 and lamivudine, another cytidine analogue (Bethell, 2004). While plasma levels and the entry of SPD754 and lamivudine into peripheral blood mononuclear cells (PBMCs) were unaffected by each other's presence, lamivudine reduced intracellular SPD754 triphosphate (TP) concentrations—the active compound—both *in vitro* and *in vivo*. "Levels of SPD754-

TP were practically undetectable," Dr. Eron explained. "As these new NRTIs are being developed, we're going to have to insist that the pharmaceutical companies do the appropriate plasma and intracellular PK analyses. This is a good example of a study being done at the right time, before conducting larger studies. It's important that we get other companies to follow this example."

SN1212/SN1461

WHILE THERE HASN'T YET BEEN MUCH IN THE WAY OF *IN VIVO* DATA TO SUPPORT its potential use, there is a great deal of excitement surrounding *in vitro* studies of SN1212 and its oral prodrug SN1461. SN1212 is a novel mutagenic deoxyribonucleoside analogue that works in an entirely different manner than other NRTIs. It does not work as a DNA chain terminator, but instead "causes the virus to hyper mutate," explained Dr. Eron. "Giving this drug, at least *in vitro*, causes the virus to accumulate so many mutations that it essentially causes it to become replication-incompetent. It doesn't have any immediate activity, like we see with other NRTIs. It has activity after a number of replication cycles and multiple mutations have occurred."

The IC₅₀ of SN1212 is 10 nM to 100 nM. At a concentration of 320 nM, no mitochondrial toxicity was observed and no adverse events were reported in dogs receiving up to 2,000 mg per kilogram of body weight.

"The company is currently gearing up to apply for IND [Investigational New Drug] status with the FDA," Dr. Eron commented.

II. New Non-Nucleoside Reverse Transcriptase Inhibitors

TMC125

TIBOTEC'S TMC125 IS A FLEXIBLE COMPOUND THAT, AT LEAST *IN VITRO*, HAS activity against both wild-type HIV strains and those containing key mutations associated with NNRTI resistance. In antiretroviral-naïve patients, seven days of TMC125 monotherapy resulted in a 1.99 log copies/mL reduction in HIV-RNA (Gruzdev, 2003) (see Figure 2). In fact, data presented at the 9th Conference on Retroviruses and Opportunistic Infections (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).

In vitro data evaluating the effectiveness of TMC125 against a panel of

NNRTI-resistant viruses were reported at the 11th CROI in San Francisco (Vingerhoets, 2004). To put these data into context, the investigators established that the IC_{50} for TMC125 against wild-type virus was 0.9 nM. Three of 54 variants harboring single mutations known to confer at least partial resistance to the current crop of NNRTIs—Y181I, Y181V, and F227C—had a greater than tenfold reduction in sensitivity to TMC125. Of 19 variants harboring two mutations, one strain—containing V179F and Y181C—resulted in a greater than tenfold reduction in TMC125 sensitivity. More prevalent combinations of two NNRTI mutations—including L100I, K103N, Y181C, and G190A—all resulted in less than a tenfold decrease in TMC125 sensitivity. Conversely, 11/19 and 4/19 variants containing two of these key mutations had greater than tenfold and hundredfold reductions in sensitivity to efavirenz respectively. As for variants harboring three key NNRTI-associated mutations—a rare occurrence in the real world, say researchers at Virco—decreased sensitivity to TMC125 was observed, albeit to a lesser degree than efavirenz.

Data from a study evaluating the short-term effects of TMC125 in NNRTI-experienced patients with high levels of drug resistance to currently available NNRTIs have been published (Gazzard, 2003a). Sixteen patients, all of whom had between 10- and 500-fold resistance to either efavirenz (Sustiva) or nevirapine (Viramune), switched their faltering NNRTI for 18 100 mg daily TMC125 capsules (given 900 mg BID) for seven days. Twelve of the patients enrolled in this study had at least two reverse transcriptase mutations that conferred high-level resistance to both efavirenz and nevirapine. On day 8, the average decrease in HIV-RNA was 0.86 \log_{10} copies/mL, with 12 patients achieving a greater than 0.5 log reduction and seven patients achieving a greater than 1 log decline. Interestingly, no association was apparent between the observed antiviral responses and baseline resistance. Tolerability was also reported to be good, with mild headaches and diarrhea—ostensibly attributed to the inactive ingredients in the current capsule formulation—being the most common side effects reported. Overall, these results demonstrated the short-term activity of TMC-125 in NNRTI-experienced patients, albeit to a comparatively lesser degree than those seen in NNRTI-naïve patients.

Capravirine

A PROMISING NNRTI BRIEFLY DISCUSSED BY DR. ERON WAS CAPRAVIRINE (AG-1549). According to Agouron Pharmaceuticals and its parent company Pfizer, capravirine is active against HIV isolates containing single reverse transcriptase substitutions such as K103N, V106A, and L100I—three mutations that confer resistance to other NNRTIs. However, HIV with dual mutations at positions 100 and 103 resulted in a 24- to 40-fold decrease in sensitivity. The common 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 the FDA and Pfizer announced that capravirine use in clinical trials would be restricted because of animal toxicology studies demonstrating 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 patients 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 that the drug is roughly ten times more potent than any of the current NNRTIs (Hernandez, 2000). Used as monotherapy in treatment-naïve patients, capravirine (2,100 mg BID) resulted in an HIV-RNA reduction of 1.7 log copies/mL after ten days of treatment.

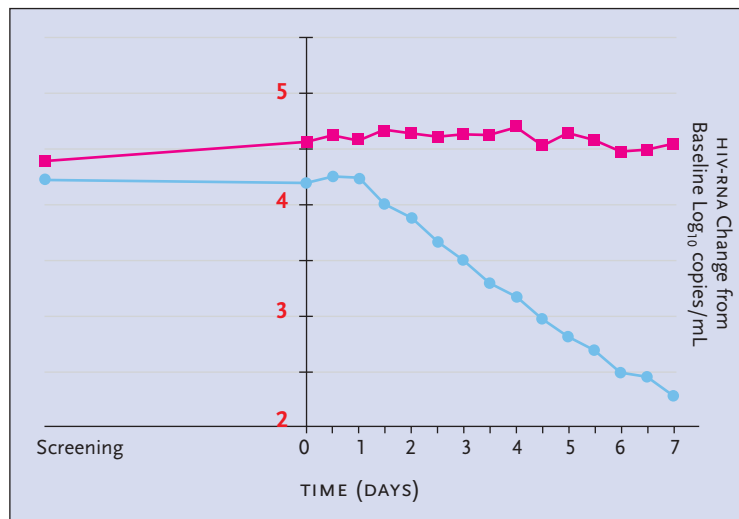


FIGURE 2. TMC 125 for Seven Days: Treatment-Naïve Patients

Source: Gruzdev, 2003

Preliminary results from a phase II clinical trial of capravirine involving 75 NNRTI-experienced patients were presented three years ago at the 8th CROI in Chicago (Wolfe, 2001). The study compared two doses of capravirine—1,400 mg BID and 2,100 mg BID—to a placebo, with all three groups of patients receiving nelfinavir and two new NRTIs. Approximately 25/50 (50%) evaluable patients who received either dose of capravirine had HIV-RNA levels below 400 copies/mL after 12 weeks of treatment. Among the 12 patients 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 patients in the 1,400 mg capravirine group, the median HIV-RNA decrease after 16 weeks was 2.2 log copies/mL. As for the 10 evaluable patients in the 2,100 mg capravirine group, the median viral load decrease was 1.7 log copies/mL after 16 weeks of treatment. In terms of adverse events, diarrhea, nausea, and vomiting occurred more frequently in the 2,100 mg group than in the 1,400 mg or placebo groups. At the time of this presentation, four patients had discontinued because of treatment failure and seven patients had discontinued because of adverse events.

Additional data from more recent capravirine studies are eagerly awaited.

III. Protease Inhibitors

Atazanavir (Reyataz)

BRISTOL-MYERS SQUIBB'S ATAZANAVIR (REYATAZ) IS A SEMI-SYMMETRICAL azapeptide agent that is well absorbed and has a half-life ranging between 2.9 and 6.5 hours. A dose of 400 mg—two 200 mg tablets once a day with food—has been approved by the U.S. Food and Drug Administration (FDA). The FDA has also approved an atazanavir dose of 300 mg—two 150 mg tablets—for use in combination with 100 mg ritonavir (Norvir), in treatment-experienced patients, in order to achieve higher plasma concentrations of atazanavir and to offset the negative interactions with efavirenz and tenofovir (Viread). “Atazanavir is very convenient, regardless of whether or not it’s given with ritonavir,” Dr. Eron said. “It’s two pills once a day, one of the easiest protease inhibitors available.”

There have been a number of studies indicating that patients receiving atazanavir-based regimens in clinical trials have not experienced significant increases in triglyceride or cholesterol levels—an encouraging observation in light of the metabolic complications that have been seen in patients taking any of the currently approved protease inhibitors. “When atazanavir is given with ritonavir, it’s still not clear what effect this combination has on lipids, at least in patients who are new to protease inhibitor therapy,” Dr. Eron commented. “We don’t have all the data yet.”

In terms of its effectiveness, a pair of phase II clinical trials comparing atazanavir and two NRTIs to nelfinavir and two NRTIs found that both regimens yielded comparable results (Sanne, 2003; 2001).

To put its first-ever protease inhibitor contender to the ultimate test, Bristol-Myers Squibb conducted a large phase III clinical trial (BMS A1424-034) comparing atazanavir to its very own efavirenz, a drug that has a history of performing extraordinarily well in clinical trials (Squires, 2004). Eight-hundred antiretroviral-naïve patients in North America, South America, Europe, Asia, and Africa were randomized to receive either of these drugs in combination with zidovudine and lamivudine. At baseline, the median viral load was 4.9 log₁₀ copies/mL and the median CD4+ count was 282 cells/mm³. 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 intent-to-treat analysis demonstrated that 70% of patients in the atazanavir group and 64% of patients in the efavirenz group had HIV-RNA levels below 400 copies/mL. Employing the more sensitive viral load assay, it was determined that 32% of patients in the atazanavir group and 37% of patients in the efavirenz group had HIV-RNA levels below 50 copies/mL. [EDITOR’S NOTE: *There has been some concern regarding the low percentage of responders, in both groups, using the <50 copies/mL cutoff. One explanation may lie in the approach to the intent-to-treat analysis. Patients were permitted to either reduce the dose of the NRTIs—or switch to another NRTI [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 patients 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 coded as failures in the intent-to-treat analysis. Another possible explanation involves the type of blood collection tube used in this study [PPT tubes, compared to standard EDTA tubes]. In a post-study laboratory assessment, samples collected in EDTA tubes were more likely to yield a higher percentage of undetectable viral load titers—using the 400 and 50 copies/mL cutoffs—than samples collected in PPT tubes.*]

As for the efficacy of atazanavir in treatment-experienced patients, 48-week follow-up data have been presented (DeJesus, 2004). Study A1424-045 is an ongoing, randomized, multicenter trial comparing three treatment groups: 1) atazanavir (300 mg QD) plus ritonavir (100 mg QD); 2) atazanavir (400 mg QD) plus saquinavir (Fortovase) (1200 mg QD); and 3) lopinavir/ritonavir (Kaletra) (400/100 mg QD). All patients are also receiving tenofovir plus another NRTI.

Prior to study entry, patients were required to have failed two antiretroviral regimens, at least one of which had to be a protease inhibitor-containing regimen. The mean time of prior antiretroviral use was 139 weeks for PIs, 283 weeks for NRTIs, and 85 weeks for NNRTIs. Most patients had taken a nelfinavir-based regimen and then changed to an NNRTI-based regimen. Two-thirds of the patients entered the study on an NNRTI-based regimen. The mean CD4+ count at baseline was 338 cells/mm³ and the mean viral load was 4.4 log₁₀ copies/mL.

Generally speaking, atazanavir/ritonavir and lopinavir/ritonavir were similar for the primary efficacy outcome measure of time-averaged difference in the change from baseline HIV-RNA levels. However, this

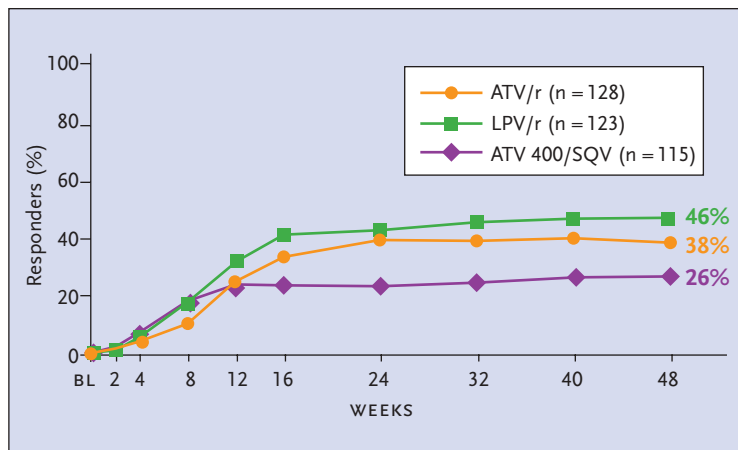


FIGURE 3. BMS-035: Virologic Response (< 50 copies/mL) Through 48 Weeks

Source: DeJesus, 2004

study was not large enough to reach a definitive conclusion that atazanavir/ritonavir and lopinavir/ritonavir are equivalent on the secondary outcome measure of undetectable viral loads.

After 48 weeks of treatment, the mean change in viral load was -1.58 log₁₀ copies/mL in the atazanavir/ritonavir group and -1.70 log₁₀ copies/mL in the lopinavir/ritonavir group. Approximately 38% had HIV-RNA levels below 50 copies/mL in the atazanavir/ritonavir group and approximately 45% had HIV-RNA levels below 50 copies/mL in the lopinavir/ritonavir group (see Figure 3). As for CD4+ count changes, patients in the atazanavir/ritonavir group saw an increase of 116 cells/mm³ after 48 weeks, compared to an increase of 123 cells/mm³ in the lopinavir/ritonavir group.

The mean viral load change from baseline among patients receiving atazanavir/saquinavir was -1.55 log₁₀ copies/mL, and the time-averaged difference in the viral load change compared to those in the lopinavir/ritonavir group was 0.33. The average CD4+ count increase was 72 cells/mm³. And after 48 weeks of treatment, the proportion of patients in the atazanavir/saquinavir group with viral loads below 400 copies/mL and 50 copies/mL was 38% and 26% respectively. In other words, compared with atazanavir/ritonavir and lopinavir/ritonavir, coadministration of atazanavir and saquinavir proved to be an inferior mix.

While Study 045 is rightly referenced as an evaluation of atazanavir/ritonavir in protease inhibitor-experienced patients, it is important to stress that most patients had taken only nelfinavir- and NNRTI-based regimens prior to enrollment in this study. It’s not clear if these results can be applied to more heavily protease inhibitor-experienced patients.

The effects of atazanavir/ritonavir on lipid levels were also recorded in this study. At baseline, total cholesterol levels were 215 mg/dL in the atazanavir/ritonavir group and 196 mg/dL in the lopinavir/ritonavir group. After 48 weeks of treatment, total cholesterol was reduced by 8% in the atazanavir/ritonavir group and increased by 6% in the lopinavir/ritonavir group. LDL cholesterol levels decreased by 10% in the atazanavir/ritonavir group and increased by 1% in the lopinavir/ritonavir group.

Atazanavir’s resistance profile has become much clearer over the past few years. Atazanavir-resistant clinical isolates—documented in antiretroviral-naïve patients experiencing virologic failure while on an initial atazanavir-based regimen—harbored the unique 150L mutation, often in combination with an A71V mutation. In these patients, the 150L mutation

was associated with phenotypic resistance to atazanavir, but retained *in vitro* susceptibility to other protease inhibitors (e.g., amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). However, there are no clinical data available to demonstrate the effect of the 150L mutation on the efficacy of subsequently administered protease inhibitors.

“I think we can safely say that the 150L mutation does not result in cross-resistance to other protease inhibitors,” Dr. Eron commented. “This is good news for patients who use atazanavir as their first protease inhibitor, though we don’t know as yet whether the 150L mutation will be the predominant mutation observed when patients rebound on initial therapy with atazanavir/ritonavir-containing regimens. As for the use of atazanavir after other protease inhibitors have failed, the 150L mutation shouldn’t be much of an issue. We could see the 150L mutation arise in some of our treatment-experienced patients, but most acquire protease inhibitor-associated mutations along the more standard pathway, which doesn’t usually include 150L.” However, it’s important to note that no clinical data is yet available for patients who fail atazanavir and then go on to other protease inhibitor-based regimens.

Important issues for all clinicians to consider include the negative drug-drug interactions between atazanavir and antacids, H₂ blockers, and proton pump inhibitors. Atazanavir requires an acid environment for absorption; drugs that reduce stomach acid should not be used concomitantly. “We still don’t know if ritonavir boosting can overcome the effect of these drugs on atazanavir levels,” Dr. Eron stressed. As discussed above, coadministration of atazanavir with tenofovir and/or efavirenz can be problematic, necessitating that the atazanavir/ritonavir dosing schedule be used. “We don’t have any data yet regarding the effect of atazanavir/ritonavir coadministration on lipid levels in treatment-naive patients, although the data in treatment-experienced patients certainly are encouraging,” Dr. Eron said. “We also need to see more efficacy data in patients who are protease inhibitor-naive but are resistant to lamivudine.”

Fosamprenavir (Lexiva)

DR. ERON SPENT SOME TIME DISCUSSING FOSAMPRENAVIR (LEXIVA), GlaxoSmithKline’s amprenavir prodrug approved by the FDA in October 2003.

The results of two open-label studies involving antiretroviral-naive patients have been reported. In the first study, APV30001 (the NEAT study), 249 patients were randomized to receive twice-daily fosamprenavir (1,400 mg BID) or twice-daily nelfinavir (1,250 mg BID) in combination with twice-daily abacavir and lamivudine (Rodriguez-French, 2004). Rates of virologic failure were higher in the nelfinavir group (32%) than in the fosamprenavir group (19%)—most notably among patients with high baseline HIV-RNA levels—after 48 weeks of therapy. “This involved taking two pills of fosamprenavir twice a day, and rates of hyperlipidemia were lower in the fosamprenavir group,” Dr. Eron added.

In Study APV30002 (the SOLO study), another open-label comparison, once-daily fosamprenavir plus ritonavir (1,400 mg/200 mg QD) was compared to twice-daily nelfinavir (1,250 mg BID) in 649 treatment-naive patients (Gathe, 2004). Again, both groups of patients received twice-daily abacavir and lamivudine. In this study, response rates were similar: 58% of patients in the fosamprenavir/ritonavir had HIV-RNA levels below 50 copies/mL after 48 weeks, compared to 55% in the nelfinavir group. However, virologic failures were more common among patients in the nelfinavir group than in the fosamprenavir/ritonavir group (16% vs. 6% respectively).

“In this study, there was a more noticeable effect of fosamprenavir on lipid levels, probably because of coadministration with ritonavir,” Dr. Eron

pointed out. “However, what was really interesting about this study was the low level of genotypic resistance to fosamprenavir or the NRTIs after 48 weeks. Genotypic resistance, meaning the presence of mutations, was much more common among patients failing in the nelfinavir group.” To be exact, of 32 patients allotted to receive fosamprenavir/ritonavir and participating in a virology substudy, none had primary or secondary protease mutations after 48 weeks (MacManus, 2004). Conversely, in the nelfinavir group, 30/54 (56%) evaluable patients had either primary or secondary mutations associated with protease inhibitor resistance. Rates of reverse transcriptase mutations were lower in the fosamprenavir/ritonavir group as well: 9% vs. 57%.

As for fosamprenavir in treatment-experienced patients, there was Study APV30003. This study was a randomized, open-label comparison of two different fosamprenavir/ritonavir regimens (700 mg/100 mg BID or 1,400 mg/200 mg QD) vs. lopinavir/ritonavir (400 mg/100 mg BID) in 315 patients who had failed one or two prior PI-based regimens. The time-averaged changes in viral load from baseline after 48 weeks was $-1.4 \log_{10}$ copies/mL for fosamprenavir/ritonavir BID and $-1.67 \log_{10}$ copie/mL for the lopinavir/ritonavir group (fosamprenavir package insert). The proportions of patients who achieved and maintained undetectable viral loads (less than 50 copies/mL) were 46% in the fosamprenavir/ritonavir BID group and 50% in the lopinavir/ritonavir group.

It’s important to note that this study was not large enough to reach a definitive conclusion that fosamprenavir/ritonavir and lopinavir/ritonavir are clinically equivalent. But if one thing is clear, it is that once-daily fosamprenavir/ritonavir should not be used in PI-experienced patients. After 48 weeks in this study, only 37% of patients in the once-daily fosamprenavir/ritonavir group had HIV-RNA levels below 50 copies/mL—a clear-cut inferior finding when compared to the response rates seen with either fosamprenavir/ritonavir BID or lopinavir/ritonavir.

“One problem with fosamprenavir is the drug-drug interactions issue,” Dr. Eron said. “For example, if you give a patient fosamprenavir plus Kaletra, lopinavir and amprenavir levels decrease. Plus, fosamprenavir can be difficult to take with zidovudine. Gastrointestinal toxicity is common and there’s very little information regarding the use of fosamprenavir with non-GlaxoSmithKline NRTIs. So I haven’t exactly figured out how to use fosamprenavir in experienced patients in my practice.”

Tipranavir

TIPRANAVIR IS A NONPEPTIDIC DIHYDROPYRONE, A NEW CLASS OF PROTEASE INHIBITORS believed to have greater flexibility in conforming to enzyme variants resistant to current protease inhibitors. The compound was originally developed by Pharmacia & Upjohn and has since been taken over by Boehringer Ingelheim.

As with its unique chemical structure, tipranavir also differs from other currently available protease inhibitors in its metabolic profiles. The drug induces the cytochrome P₄₅₀ pathway, whereas current protease inhibitors either inhibit or both inhibit and induce this enzyme system. In early phase II studies, a whopping 1,500 mg of tipranavir, taken three times daily, was required to achieve the necessary trough concentration. To circumvent this hurdle, the manufacturer developed a self-emulsifying drug delivery system (SEDDS)—a soft-gel capsule—for the compound. After taking the new formulation of tipranavir into a phase II study (Study 1182.52), the manufacturer recently concluded that the optimal tipranavir dose is 500 mg twice daily and will need to be combined with low doses of ritonavir (200 mg twice daily) to reverse the rapid metabolism of the drug by cytochrome P₄₅₀ and to allow dosing with food (Gathe, 2003).

Study 1182.52 has also produced some important resistance data (Cooper, 2003). In this study, patients who had tried at least two protease inhibitors in the past and had strains of HIV harboring at least one common protease-associated mutation (PRAM)—L33I/V/F, V82F/L/T, I84V, or L90M—were randomized to receive one of three tipranavir doses in combination with ritonavir (see dose-optimization conclusions above). According to phenotypic analyses of 157 isolates collected at the start of the study (216 patients were enrolled), the median fold increases in IC_{50} ranged from 7.0 to 94.2 for all of the currently approved protease inhibitors, compared to a 1.1-fold increase in the tipranavir IC_{50} against these highly resistant isolates. Tipranavir's IC_{50} increase was onefold or less in 42% of the isolates, between onefold and twofold in 27% of the isolates, between twofold and fourfold in 18%, and greater than fourfold in 12%. Among patients harboring HIV strains with twofold or less resistance to tipranavir, viral load decreased, on average, by 1.23 log copies/mL during the first month of the study. Among patients with greater than twofold resistance to tipranavir, median viral load decreases were less than 0.25 log copies/mL. In other words, a greater than twofold increase in tipranavir's IC_{50} was a breakpoint for the drug. However, the investigators noted that an accumulation of a large number of protease gene mutations was necessary to result in a significant diminished antiviral response to tipranavir. "According to the data analysis, patients with three or more PRAMS were not likely to benefit from tipranavir therapy," Dr. Eron commented. "However, we now know from subsequent studies that this turned out to be a flawed conclusion."

One of the subsequent studies of interest is Study 1182.51 (Leith, 2004). This open-label study evaluated the pharmacokinetics of tipranavir/ritonavir alone and in combination with saquinavir, amprenavir, or lopinavir/ritonavir (Kaletra) in 315 highly treatment-experienced patients with three or more PRAMS prior to study entry. The following groups were compared: 1) tipranavir/ritonavir 500 mg/200 mg twice daily plus an optimal background regimen (OBR); 2) saquinavir/ritonavir 1000 mg/100 mg twice daily plus OBR; 3) amprenavir/ritonavir 600 mg/100 mg twice daily + OBR; or 4) lopinavir/ritonavir 400 mg/100 mg twice daily + OBR. After two weeks, tipranavir/ritonavir 500 mg/100 mg twice daily was added to the groups that didn't initially receive tipranavir. Minimum concentrations (C_{min}) were evaluated at the end of weeks 1, 2, 3, and 4, and a 12-hour intensive pharmacokinetics evaluation was conducted both before and after addition of tipranavir to the other protease inhibitors.

Because of its unique metabolism requirements, it came as no surprise that tipranavir reduced the C_{min} values of amprenavir, saquinavir, and lopinavir by 56%, 55%, and 81% respectively. As a result, after four weeks of double-boosted PI therapy, HIV-RNA values turned toward baseline values in all study groups. Based on these results—and until double-boosted PI optimization studies are conducted—it is not recommended that tipranavir be used in combination with any other PIs, with the exception of ritonavir.

"What is encouraging about this study is the viral load drop, approximately 1.2 logs, that was seen in these patients," Dr. Eron commented. "Keep in mind, this was a highly treatment-experienced population. All of the patients had more than three PRAMS. The .52 study suggested that greater than three PRAMS would greatly limit tipranavir activity, whereas the .51 study demonstrated significant activity. So this is very good news for any of us treating patients with a lot of protease inhibitor experience."

TMC114

MUCH LIKE ITS NNRTI CONTENDER TMC 125 (DISCUSSED ABOVE), TIBOTEC dubs TMC114—its lead protease inhibitor candidate—a "resistant-repellent" 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 prior therapy with other protease inhibitors.

A dose-escalating study of TMC114 has been conducted (Van der Geest, 2001). Two groups of nine HIV-negative volunteers (six active, three placebo) received alternating doses of 100 mg, 200 mg, 400 mg, 800 mg, 1,200 mg, or 1,600 mg. Because the maximum tolerated dose was not reached, an additional panel was added to receive 2,400, 3,200 and 4,000 mg. Initially, plasma concentrations increased more than proportionally with the dose. No further increases in plasma concentrations were observed between 2,400 mg and 3,200 mg. The mean C_{max} was 14.4–15.3 mg/ml at these dose levels. The elimination half-life was approximately ten hours, irrespective of dose. For 800 mg doses and higher, plasma levels at eight to 12 hours post-dose exceeded protein-adjusted IC_{50} s for isolates resistant to currently approved protease inhibitors. All doses were considered safe. Diarrhea—because of polyethylene glycol (PEG) in the formulation—occurred at high dose levels and limited further escalation. Short-term localized oral and peripheral paresthesias were observed in 3/6 (50%) volunteers receiving the 3,200 mg TMC114 dose.

In a phase IIa clinical trial reported at the 11th CROI, 50 patients failing a protease inhibitor-based regimen—and a history of other protease inhibitor failures in the past—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 (Peeters, 2004). At baseline, patients had a median viral load of 4.3 log copies/mL and 46% were resistant to all of the currently approved protease inhibitors. After 14 days, the patients 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 1.3 copies/mL respectively. Not surprisingly, no patients in the control group achieved undetectable viral load levels (<400 copies/mL); after 14 days of treatment, in 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.

Tibotec's next step will be to conduct a dose-finding study using a solid formulation of TMC114. Phase II studies are in progress.

IV. Entry and Fusion Inhibitors

SINCE 1996, WHEN THE ELUSIVE CD4+ CELL CORECEPTORS CCR5 AND CXCR4 were discovered, the process by which HIV gains entry into these cells has been a major focus of basic and clinical research. What we now know about this process is much more complete, and understanding this complicated process has led to the development of inhibitors for each step of HIV entry.

The HIV entry process begins with successive interactions between the trimeric envelope complex—a cluster of proteins on HIV's outer coat, sometimes referred to as the gp160 spike—and both CD4 and a chemokine coreceptor (either CCR5 or CXCR4) on the cell surface. This complex is made up of three transmembrane glycoproteins (gp41), which anchor the cluster to the virus, and three extracellular glycoproteins (gp120), which contain the binding domains for both CD4 and the chemokine receptors.

The first step in fusion involves the high-affinity attachment of the CD4 binding domains of gp120 to the N-terminal membrane-distal domain of CD4. Once bound, the envelope complex undergoes a structural change, bringing the chemokine binding domains of gp120 into proximity with the chemokine receptor on the CD4+ cell surface, allowing binding for a more stable two-pronged attachment.

With the virus now latched on to both CD4 and the chemokine receptor, additional conformational changes take place in the envelope complex, whereby gp41, originally tucked away within the trimeric complex, is exposed and the N-terminal fusion peptide of gp41 pierces the CD4+ cell's membrane. From there, two heptad repeat sequences (HR1 and HR2) of gp41 interact by folding in on themselves, resulting in collapse of the extracellular portion of gp41 to form a hairpin, which is sometimes referred to as a coiled-coil bundle. The hairpin structure brings the virus and cell membrane close together, allowing fusion of the membranes and subsequent entry of the virus core.

While additional details of this multistep process are still being worked out in the lab, enough has been learned about the three major steps involved in HIV entry—the binding of gp120 to CD4, the binding of gp41 to either CCR5 or CXCR4, and the formation of gp41 fusion determinants that allows the virus to fuse with its cellular target—to develop therapeutic strategies targeting each of these steps. Indeed, a number of compounds are in various stages of development. For individuals with HIV resistant to any or all of the current inhibitors of reverse transcriptase and protease, these fusion and entry inhibitors represent truly unique classes of drugs.

This section briefly summarizes some compounds, in the early stages of development, that may expand the fusion and entry inhibitor horizon beyond the first approved HIV entry inhibitor, the fusion inhibitor enfuvirtide (Fuzeon).

PRO 542

PROGENICS PHARMACEUTICALS' PRO 542—ALSO KNOWN AS CD4-IGG2—is a soluble CD4 receptor complex 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 that can be synthesized using monoclonal antibody technology. As with enfuvirtide, PRO 542 cannot be taken orally; it must be infused, either intravenously or subcutaneously.

A 2001 report, published in the *Journal of Infectious Diseases*, indicated that PRO 542 and enfuvirtide are synergistic against a diverse panel of virus over a broad range of drug concentrations (Nagashima, 2001). In some cases, the individual doses of both enfuvirtide and PRO 542 were able to be reduced by tenfold or more.

Results from phase I/II clinical trials of PRO 542 involving HIV-positive 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 peak serum concentrations increased linearly with dose, and a terminal serum half-life of three to four days was observed, indicating that daily administration may not be necessary. No patient developed antibodies to PRO 542. Transient HIV-RNA decreases were reported after single-dose administration.

In the phase I/II study enrolling 18 HIV-positive children, PRO 542 was evaluated by single and multidose intravenous infusions (Shearer, 2000). The drug was well tolerated, and, as with the adults, dose proportionality was observed in terms of AUC and PEG serum concentrations. Noticeable decreases of approximately 0.7 log copies/mL in plasma

HIV-RNA levels were seen in four of the 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.

In a more recent study published earlier this year, 12 HIV-infected individuals were treated with a single dose of PRO 542 (25 mg/kg) and then monitored for six weeks (Jacobson, 2004). At the dose used, PRO 542 was well tolerated and demonstrated a serum half-life of three days. Statistically significant acute reductions in HIV-RNA levels were observed across all study patients, and greater antiviral effects were observed in a cohort of patients with more advanced HIV disease (defined as viral loads greater than 100,000 copies/mL and CD4+ counts below 200 cells/mm³). In these patients with advanced disease, PRO 542 maintained a 0.5 log₁₀ copies/mL reduction in HIV-RNA for four to six weeks post-treatment. In addition, a significant correlation was observed between antiviral effects observed *in vivo* and viral susceptibility to PRO 542 *in vitro*.

Other phase II clinical trials, which are being conducted in adults and children, are currently under way. These studies will include patients with HIV resistant to current antiretroviral options. The drug is currently being evaluated in an improved formulation for subcutaneous administration.

SCH 417690 (SCH-D)

SCH 417690, FORMERLY KNOWN AS SCH-D, IS SCHERING-PLOUGH'S SECOND CCR5 antagonist contender to enter into clinical trials, following in the footsteps of SCH-C, which has been discontinued because of toxicity concerns.

Phase I clinical trial results, involving 48 HIV-infected patients with CCR5-tropic virus receiving various doses of the drug, were reported at the 11th CROI (Schurmann, 2004). Sixteen patients were randomized into each once-daily dosing group (10 mg, 25 mg, 50 mg, or placebo) evaluating oral SCH 417690 monotherapy for 14 days (four patients in each dosing group received placebo). All patients were either naive to antiretroviral therapy or had been off treatment for at least eight weeks.

The drug was well tolerated and no adverse events were documented. After 14 days, HIV-RNA levels were 1.08 log₁₀ copies/mL below baseline in the 10 mg group, 1.56 log₁₀ copies/mL below baseline in the 25 mg group, and 1.62 log₁₀ copies/mL below baseline in the 50 mg group (see Figure 4). Approximately 45% of patients in both the 25 mg and 50 mg groups saw their viral loads drop by at least 1.5 log₁₀ copies/mL.

Additional data has also concluded that 50 mg SCH 417690 achieves more substantial plasma concentrations than 50 mg SCH-C.

ACTG 5211, a phase II study of SCH 417690 with ritonavir and optimized background antiretrovirals in treatment-experienced patients, is actively enrolling patients.

BMS-488043

AN ORAL GP120/CD4 BINDING INHIBITOR EXPECTED TO ENTER PHASE II testing is BMS-488043, being developed by Bristol-Myers Squibb. The antiviral activity, safety, and tolerability of this drug were evaluated in a placebo-controlled multiple-dose study in HIV-infected patients (Hanna, 2004). Two groups of 15 patients—all of whom were either naive to antiretroviral therapy or had been off treatment for at least 16 weeks—received 800 mg or 1,800 mg doses of BMS-488043 or placebo, every 12 hours for eight days with a high-fat meal. On the eighth day of treatment, the average reductions in HIV-RNA were 0.7 log₁₀ copies/mL in the 800 mg group and 1.0 log₁₀ copies/mL in the 1,800 mg group. Among patients in

the 800 mg group, 58% experienced viral load reductions in excess of 1 log₁₀ copies/mL; in the 1,800 mg group, the rate was 67%. CD4+ count increases were more pronounced in the 800 mg group (+106 cells/mm³) than in the 1,800 mg group (+48 cells/mm³). There were no serious adverse events and no discontinuations from the study.

“While BMS is very encouraged by these results,” Dr. Eron commented, “my gut sense is that they’re going to go back and find an inhibitor that is more broadly reactive against multiple envelope types.” [EDITOR’S NOTE: As this issue of The PRN Notebook went to press, we learned that Bristol-Myers Squibb has, in fact, terminated development of BMS-488043 in the pursuit of potentially more broadly active compounds.]

UK-427,857

LIKE SCH 417690, UK-427,857 IS A CHEMOKINE RECEPTOR ANTAGONIST designed to block the CCR5 receptor. The drug is being developed by Pfizer Pharmaceuticals.

Preliminary results of a phase I study were presented at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy in 2003 (Pozniak, 2003). In this study, 24 HIV-positive individuals with CCR5-tropic virus were randomized to receive once-daily oral doses of UK-427,857 (25 mg QD or 100 mg BID) or placebo monotherapy for 14 days. Steady-state drug levels were achieved after seven days, with the best plasma concentrations achieved when taken in the fasted state. After 14 days, an average 1.4 log₁₀ copies/mL reduction in HIV-RNA was seen in patients receiving UK-427,857 100 mg BID, compared to a 0.4 log₁₀ copies/mL reduction among patients receiving the 25 mg QD dose. The drug was well tolerated; no serious adverse events were reported.

I think these and other CCR5 antagonists are very, very interesting,” Dr. Eron added. “However, drug development is going to be somewhat tricky, given that these drugs are only active against viruses that use the CCR5 receptor. They won’t be active against viruses that use the CXCR4 receptor. And there is some concern that using a CCR5 inhibitor will cause an NSI-to-SI switch, leading to a more pathogenic virus. While scientists think that the risk of this is low, it’s important to remember that scientists don’t treat HIV-positive patients. This is an issue that will need to be explored fully in clinical trials.”

AMD3100 and AMD070

AMD3100 AND AMD070 ARE BOTH CXCR4 ANTAGONISTS FROM ANOFMED INC. Because of toxicity concerns and limited efficacy, the development of AMD3100 was halted in May 2001. The company is now focused on AMD070, a compound that strongly inhibits viral infection by all CXCR4-using virus—including virus using CXCR4 alone and/or virus using both CXCR4 and CCR5—in vitro. AMD070 is orally bioavailable in animals, shows additive or synergistic effects in vitro with other antiretroviral agents, and has yielded safe results in a recent Phase Ia dose-ranging study involving HIV-negative volunteers (Stone, 2004).

A Phase IIa study is being conducted by the Adult AIDS Clinical Trials Group (AACTG 5210).

V. Integrase Inhibitors

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, de-

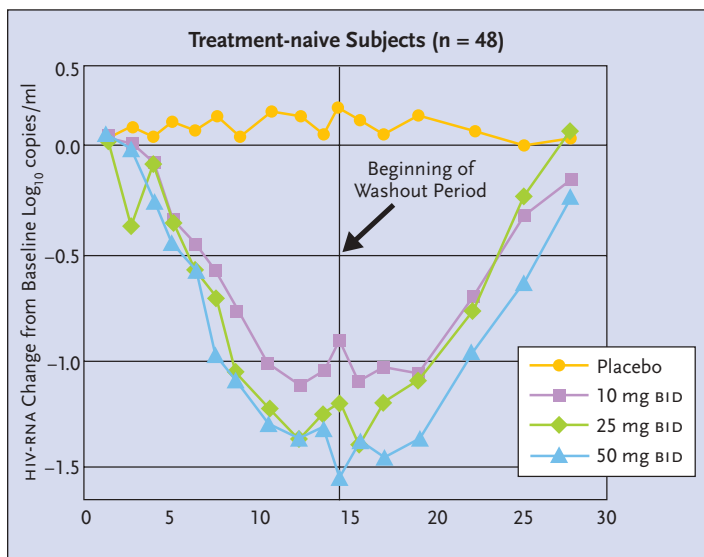


FIGURE 4. Activity of SCH 417690 (SCH-D)

Source: Schurmann, 2004

spite 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 nonselectivity, 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 (Mg⁺⁺) that is bound in the active site of the integrase gene by three acidic residues of the protein chain. Once the gene has been inhibited, the HIV-DNA forms inactive, unstable circular structures, and the virus is unable to replicate. Two earlier enzymatic functions of the integrase gene—assembly of pre-integration complexes and 3’ processing of the viral DNA ends—are not inhibited by diketo acids. They specifically inhibit the third step—strand transfer of viral DNA to cellular DNA.

S-1368 is a diketo acid being developed by Shinogi Pharmaceuticals and GlaxoSmithKline. It is a follow-up molecule to the companies’ early contender, S-1360, which was compromised by significant protein binding. “S-1368 has significantly improved in vitro activity, compared with S-1360,” Dr. Eron commented. “What’s needed is some clinical trial data, which we will hopefully have soon.”

There are also the naphthyridine 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 SHIV/HIV virus. SHIV-RNA was reduced by 1 to greater than 3 log₁₀ copies/mL 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 (Hazuda, 2004).

Despite the structural differences between S-1360 and L-870,810, 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).


VI. Maturation Inhibitors

HIV ASSEMBLY, MATURATION, AND BUDDING HAVE LONG BEEN FOCUSES of drug development efforts. Maryland-based Panacos Pharmaceuticals has been developing PA-457, a “maturation inhibitor” that hinders a late step in gag processing involving conversion of the capsid precursor (p25) to mature capsid protein (p24) (Li, 2003). As a result, newly released viral particles are defective and non-infectious.

Data from a Phase I clinical trial—involving HIV-negative study volunteers—evaluating the safety and pharmacokinetics of PA-457 were presented at the xv International AIDS Conference in Bangkok (Martin, 2004). Four doses were selected for evaluation: 25 mg, 50 mg, 100 mg, and 250 mg. At each dose level, six subjects received PA-457 and two additional individuals received placebo. The drug was well tolerated at all doses, with good oral bioavailability and favorable pharmacokinetics. All doses produced mean circulating plasma levels which exceeded the target therapeutic concentration. At doses of 50 mg or higher, drug levels continued to exceed the target concentration twenty four hours after administration. These results suggest that PA-457 will be suitable for once-daily oral dosing.

Additional Phase I studies are currently being conducted.

Conclusion

IN SUMMATION, DR. ERON STRESSED THAT WHILE THERE MAY NOT BE AS many agents in the pipeline as there have been in years past, there are definitely a few compounds that may prove to be of advantage to antiretroviral-naïve and treatment-experienced patients. The objectives of new drug development are pretty much the same as they ever were: increased potency, the ability to overcome virus resistant to currently available agents, and improved convenience and tolerability. And while it is undoubtedly true that the clinical development of new drugs can be challenging, a continued sense of cautious optimism that the therapeutic options will meaningfully expand is warranted. 

References

Bethell R, Adams J, De Muys J, et al. Pharmacological evaluation of a dual deoxycytidine analogue combination: 3TC and SP754 [Abstract 138]. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2004.

Cahn P, Lange J, Cassetti I, et al. Anti HIV-1 activity of SP754 a new NRTI: Results of a 10 day monotherapy study in treatment naïve HIV patients [Abstract LB15]. 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment, Paris, 2003.

Colonna RJ, Rose R, Cianci C, et al. Emergence of atazanavir resistance and maintenance of susceptibility to other PIs is associated with an I50L substitution in HIV protease [Abstract 597]. 10th Conference on Retroviruses and Opportunistic Infections, Boston, 2003.

Colonna RJ, Friberg J, Rose RE, et al. Identification of amino acid substitutions correlated with reduced atazanavir susceptibility in patients treated with atazanavir-containing regimens [Abstract 4]. xi International HIV Drug Resistance Workshop: Basic Principles and Clinical Implications, Seville, 2002.

Cooper D, Hall D, Jayaweera D, et al. Baseline phenotypic susceptibility to tipranavir/ritonavir is retained in isolates from patients with multiple protease inhibitor experience (bi 1182.52) [Abstract 596]. 10th Conference on Retroviruses and Opportunistic Infections, Boston, 2003.

DeJesus E, Grinsztajn B, Rodriguez C, et al. Efficacy and safety of atazanavir with ritonavir or saquinavir vs lopinavir/ritonavir in patients who have experienced virologic failure on multiple HAART regimens: 48-week results from BMS A1424-045 [Abstract 547]. 11th Conference on Retrovirus and Opportunistic Infections, San Francisco, 2004.

DeJesus E, Herrera G, Teofilo E, et al. Efficacy and safety of abacavir (ABC) versus zidovudine (ZDV) in antiretroviral therapy naïve adults with HIV-1 infection (Study CNA30024) [Abstract H-446]. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, 2003.

Gathe JC Jr, Ives P, Wood R, et al. 48-week efficacy and safety comparison of once-daily fosamprenavir/ritonavir versus twice-daily nelfinavir in naïve HIV-1 infected patients. *AIDS* 18(11):1529-37, 2004.

Gathe JC Jr, Kohlbrenner VM, Pierone G, et al. Tipranavir/ritonavir demonstrates potent efficacy in multiple protease inhibitor experienced patients: bi 1182.52 [Abstract 179]. 10th Conference on Retroviruses and Opportunistic Infections, Boston, 2003.

Gazzard BG, DeJesus E, Cahn P, et al. Abacavir once-daily (OAD) plus lamivudine (3TC) OAD in combination with efavirenz (EFV) OAD is well-tolerated and effective in the treatment of antiretroviral therapy (ART) naïve adults with HIV-1 infection (ZODIAC Study: CNA30021) [Abstract H-1722b]. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, 2003.

Gazzard BG, Pozniak AL, Rosenbaum W, et al. An open-label assessment of TMC125-a new, next-generation NRTI, for 7 days in HIV-1 infected individuals with NRTI resistance. *AIDS* 17:F49-54, 2003a.

Geleziunas R, Gallagher K, Zhang H, et al. HIV-1 resistance profile of the novel nucleoside reverse transcriptase inhibitor beta-D-2',3'-dideoxy-2',3'-didehydro-5-fluorocytidine (Reverset). *Antivir Chem Chemother* 14(1):49-59, 2003.

Gruzdev B, Rakhmanova A, Doubovskaya E, et al. A randomized, double-blind, placebo-controlled trial of TMC125 as 7-day monotherapy in antiretroviral naïve, HIV-1 infected subjects. *AIDS* 17:2487-94, 2003.

Hanna G, Lalezari J, Hellinger J, et al. Antiviral activity, safety, and tolerability of a novel, oral small-molecule HIV-1 attachment inhibitor, BMS-488043, in HIV-1-infected subjects [Abstract 141]. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2004.

Hazuda DJ, Young SD, Guare JP, et al. Integrase inhibitors and cellular immunity suppress retroviral replication in rhesus macaques. *Science* 305(5683):528-32, 2004.

Hazuda DJ. The potential for cross resistance between S-1360, L-870810 and other structurally diverse inhibitors of HIV-1 integrase strand transfer [Abstract 140]. 10th Conference on Retroviruses and Opportunistic Infections, Boston, 2003.

Hazuda DJ. Integrase inhibitors [Abstract MoOrA137]. xiv International AIDS Conference, Barcelona, 2002.

Hernandez J, Amador L, Amantea M, et al. Short-course monotherapy with ag1549, a novel nonnucleoside reverse transcriptase inhibitor, in antiretroviral naïve patients [Abstract 669]. 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2000.

Jacobson JM, Israel RJ, Lowry I, et al. Treatment of advanced human immunodeficiency virus type 1 disease with the viral entry inhibitor PRO 542. *Antimicrob Agents Chemother* 48:423-9, 2004.

Jacobson JM, Lowry I, Fletcher CV, et al. Single-dose safety, pharmacology, and antiviral activity of the human immunodeficiency virus (HIV) type 1 entry inhibitor PRO 542 in HIV-infected adults. *J Infect Dis* 182(1):326-9, 2000.

Leith J, Walmsley S, Katlama C, et al. Pharmacokinetics and safety of tipranavir/ritonavir alone or in combination with saquinavir, amprenavir, or lopinavir. Interim analysis of BI1182.51 [Abstract 5.1]. 5th International Workshop on Clinical Pharmacology of HIV, Rome, 2004.

Li F, Goila-Gaur R, Salzwedel K, et al. PA-457: a potent HIV inhibitor that disrupts core condensation by targeting a late step in Gag processing. *Proc Natl Acad Sci USA* 100(23):13555-60, 2003.

MacManus S, Yates PJ, Elston RC, et al. GW433908/ritonavir once daily in antiretroviral therapy-naïve HIV-infected patients: absence of protease resistance at 48 weeks. *AIDS* 18(4):651-5, 2004.

Martin DE, Smith P, Wild CT, et al. In vitro and in vivo disposition of PA-457, a novel inhibitor of HIV-1 maturation [Abstract WePeA5644]. xv International AIDS Conference, Bangkok, 2004.

Murphy RL, Schurmann D, Beard A, et al. Potent anti-HIV-1 activity of Reverset following 10 days of monotherapy in treatment-naïve individuals [Abstract MoOrB1056]. xv International Conference on AIDS, Bangkok, 2004.

Nagashima KA, Thompson DA, Rosenfield SI, et al. Human immunodeficiency virus type 1 entry inhibitors PRO 542 and T20 are potentially synergistic in blocking virus-cell and cell-cell fusion. *J Infect Dis* 183:1121-5, 2001.

Peeters M, Van Baelen B, De Meyer S, et al. TMC114/rivirin in multiple PI-experienced patients: Correlation of baseline genotype, phenotype, pharmacokinetics, and IQ with antiviral activity at day 14 [Abstract 533]. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2004.

Piliero P, Shachoy-Clark AD, Para M, et al. A study examining the pharmacokinetics of abacavir and the intracellular carbovir triphosphate (GSK protocol CNA10905) [Abstract A-1797]. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, 2003.

Potts KE, Fujiwara T, Sato A, et al. Antiviral activity and resistance profile of ag1549, a novel HIV-1 nonnucleoside reverse transcriptase inhibitor [Abstract 12]. 6th Conference on Retroviruses and Opportunistic Infections, Chicago, 1999.

Pozniak AL, Fätkenheuer G, Johnson M, et al. Effect of short term monotherapy with UK-427,857 on viral load in HIV-infected patients [Abstract H-443]. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, 2003.

Rodriguez-French A, Boghossian J, Gray GE, et al. The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naïve HIV-1-infected patients. *J Acquir Immune Defic Syndr* 35(1):22-32, 2004.

Sankasingh S, Weverling G, van't Klooster G, et al. TMC125 monotherapy for 1 week results in a similar initial rate of decline of HIV-1 RNA as therapy with a 5-drug regimen [Abstract 5]. 9th Conference on Retroviruses and Opportunistic Infections, Seattle, 2002.

Sanne I, Piliero P, Squires K, et al. Results of a phase II clinical trial at 48 weeks (A1424-007): a dose-ranging, safety, and efficacy comparative trial of atazanavir at three doses in combination with didanosine and stavudine in antiretroviral-naïve subjects. *J Acquir Immune Defic Syndr* 32(1):18-29, 2003.

Sanne I, Cahn P, Percival L, et al. Atazanavir vs nelfinavir in combination with stavudine and lamivudine in treatment-naïve HIV-infected patients, 48-week results [Abstract I-667]. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, 2001.

Schurmann D, Rouzier R, Nougarede R, et al. SCH D: antiviral activity of a CCR5 receptor antagonist [Abstract 140Lb]. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2004.

Shearer WT, Israel RJ, Starr S, et al. Recombinant CD4-IgG2 in human immunodeficiency virus type 1-infected children: phase I/II study. The Pediatric AIDS Clinical Trials Group Protocol 351 Study Team. *J Infect Dis* 182(6):1774-9, 2000.

Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr* 36(5):1011-9, 2004.

Stone N, Dunaway S, Flexner C, et al. Biologic activity of an orally bioavailable CCR5 antagonist in human subjects [Abstract TuPeB4475]. xv International AIDS Conference, Bangkok, 2004.

Van der Geest R, Van der Sandt I, Gille D, et al. Safety, tolerability and pharmacokinetics of escalating single oral doses of TMC114, a novel protease inhibitor (PI) highly active against HIV-1 variants resistant to other PIs [Abstract I-1934]. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, 2001.

Vingerhoets J, De Baere I, Azijn H, et al. Antiviral activity of TMC125 against a panel of site-directed mutants encompassing mutations observed in vitro and in vivo [Abstract 621]. 11th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2004.

Wolfe P, Hawley P, Boccia G, et al. Safety and efficacy of capravirine versus placebo in HIV-infected patients failing a nonnucleoside reverse transcriptase inhibitor-containing regimen: results of a phase II, double-blind, placebo-controlled study [Abstract 323]. 8th Conference on Retroviruses and Opportunistic Infections, Chicago, 2001.