

View from the Pipeline: The 2003 Review of Experimental Antiretrovirals

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DESPITE THE FACT THAT 16 ANTIRETROVIRALS ARE APPROVED FOR USE IN THE United States, 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. To provide PRN with a glimpse of drugs currently snaking their way through the development pipeline—including three drugs currently being reviewed by the U.S. Food and Drug Administration (FDA) for marketing approval—Dr. Scott Hammer returned to the podium at the January 2003 PRN meeting to discuss his observations of data presented over the past few years. A summary of his presentation—along with key data presented at the 10th Conference on Retroviruses and Opportunistic Infections (CROI), held in February in Boston—is provided here.

I. New 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. Emtricitabine is currently being reviewed by the FDA—a new drug application (NDA) was filed in September 2002—and is likely to be approved as a once-daily therapy (200 mg QD). Unfortunately, patients who have already tried and failed lamivudine (Epivir) won't likely benefit from emtricitabine, given that the M184V mutation confers high-level resistance to both drugs.

Preliminary results from several phase II studies were reported in the June 2002 issue of *The PRN Notebook*, and encouraging follow-up data were recently provided at the 10th Conference on Retroviruses and Opportunistic Infections (CROI) in Boston (Wakeford, 2002; Molina, 2002).

Of particular interest to Dr. Hammer were early data from FTC-301, a phase III, 48-week, double-blind, placebo-controlled trial that is being conducted in the United States, Europe and Latin America (Saag, 2002). In this ongoing study, antiretroviral-naïve patients with viral loads between 50,000 and 100,000 copies/mL are receiving didanosine (Videx EC) and efavirenz (Sustiva) in combination with either emtricitabine or stavudine (Zerit).

Five hundred seventy-one patients have been enrolled into FTC-301. At baseline, the median viral load was 4.9 log copies/mL and the median CD4+ count was 300 cells/mm³. After 24 weeks, 10% of patients in the stavudine group and 4% of patients in the emtric-

itabine group had experienced virologic failure, defined as a viral load above 400 copies/mL. 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 patients in the stavudine group and 7% of patients in the emtricitabine group. In terms of the proportion of patients with undetectable viral loads, 87% in the emtricitabine group and 79% in the stavudine group had viral loads below 400 copies/mL [see Figure 1]. Using a more sensitive quantitative PCR, 81% in the emtricitabine group, compared to 70% in the stavudine group, had HIV-RNA levels below 50 copies/mL after 24 weeks of treatment.

Amdoxovir

AMDOXOVIR (DAPD) IS ANOTHER NRTI THAT WAS DEVELOPED BY TRIANGLE Pharmaceuticals and is now being guided through the development pipeline by Gilead Sciences. It is a novel dioxolane purine analogue that is rapidly converted by adenosine deaminase into D-dioxolane guanine (DXG), a metabolite that has potent activity against HIV and HBV.

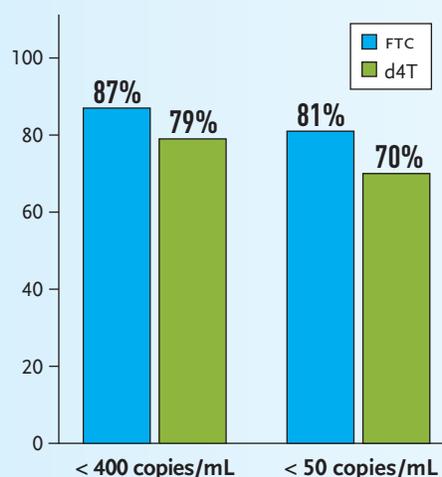
In vitro, amdoxovir has antiviral activity against zidovudine/lamivudine and stavudine/lamivudine-resistant strains of HIV and is also active against strains harboring the Q151M or the 69SS substitutions, two mutations associated with multiple-NRTI resistance. Also *in vitro*, in the presence of amdoxovir and after multiple passages of the virus, 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 in February at the 10th CROI (Thompson, 2002). Eighteen HIV-positive patients who

had been treated with approximately 11 anti-retrovirals 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 patients. While no nephrologic toxicities were reported, 5/18 (28%) patients discontinued the study because of lens opacities which, fortunately, did not have an impact on visual acuity.

Figure 1. FTC-301: Virologic Effectiveness at 24 Weeks



Source: Saag, 2001

II. New Non-Nucleoside Reverse Transcriptase Inhibitors

Capravirine

A PROMISING NNRTI DISCUSSED BY DR. Hammer 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. 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 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 to date suggested that the drug is roughly ten times more potent than any of the current NNRTIs (Hernandez, 2001). Used as monotherapy, capravirine (2,100 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 patients were presented two 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 zidovudine 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.

Figure 2. TMC125 *In vitro* Activity Against NNRTI-Resistant Mutants

		Nevirapine	Delavirdine	Efavirenz	TMC125	
HIV Strain		EC ₅₀ (nM)				
WILD TYPE	LAI(WT)	85	16	1.0	1.4	
	L100I	638	3,467	38	3	
	K101E	4,300	190	6	6	
	K103N	2,467	1,697	39	1	
	V106A	2,410	2,245	36	2	
	E138K	486	56	2	5	
	V179E	1,800	750	6	3	
	NNRTI MUTANTS	Y181C	5,351	1,336	2	7
		Y188L	6,722	187	138	5
		G190A	3,465	38	11	1
G190S		>10,000	23	344	2	
F227C		>10,000	1,200	180	27	
K103N + L100I		>10,000	>10,000	>10,000	19	
K103N + K101E		>10,000	1,500	183	3	
K103N + Y181C		>10,000	>10,000	43	4	
V106A + F227L		>10,000	164	39	4	

EC₅₀ < 10 nM

10 nM < EC₅₀ < 100 nM

EC₅₀ > 100 nM

Source: Tibotec

TMC125

TIBOTEC'S TMC125 IS A FLEXIBLE COMPOUND THAT, AT LEAST *IN VITRO*, HAS equipotent 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 [see Figure 2]. In antiretroviral-naïve patients, 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).

Also presented at the 9th CROI were the short-term effects of TMC125 in NNRTI-experienced patients with high levels of drug resistance to currently available NNRTIs (Gazzard, 2002). 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 daily TMC125 capsules (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 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.

III. Protease Inhibitors

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 has 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 IIb dose-optimization study (study 1182.52), the manufacturer recently concluded that the tipranavir dose has been set at 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).

An initial glimpse into the *in vitro* activity of tipranavir against multiple-protease inhibitor-resistant HIV strains was published by Dr. Brendan Larder and his colleagues three years ago in *AIDS* (Larder, 2000). Studied by Dr. Larder's team were 134 clinical viral isolates documented to be highly cross-resistant to currently available protease inhibitors. Of 105 isolates with more than tenfold resistance to three or four protease inhibitors—with an average of 6.1 key protease inhibitor mutations per sample—95 (90%) were susceptible to tipranavir; eight (8%) had four- to tenfold resistance to tipranavir, and only two (2%) had more than tenfold resistance.

At the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), held in September 2001 in Chicago, data from study BI 1182.4 were reported, a clinical trial comparing tipranavir (500 mg or 1250 mg BID) and saquinavir, both in combination with ritonavir and two new NRTIs (Slater, 2001). Sixty-three patients, all of whom had viral load levels above 1,000 copies/mL while receiving their first protease inhibitor-based regimen, were randomized evenly among the three groups. In an intent-to-treat analysis, the proportion of patients with HIV-RNA below 400 copies/mL was equivalent in the lower-dose tipranavir/ritonavir and the saquinavir/ritonavir arms (39% and 40%, respectively), and somewhat greater in the higher-dose tipranavir/ritonavir arm (55%) at 16 weeks.

Only 28/63 (44%) of patients participating in BI 1182.4 had HIV protease mutations at baseline. This, in turn, limited the research team's ability to match key patterns of mutations with virologic outcomes using tipranavir in a protease inhibitor-experienced population of patients—a key factor that must be addressed if the drug is to be used correctly as a component of salvage therapy. Fortunately, data presented at the 9th CROI has helped shed light on this situation (Schwartz, 2002). In this analysis, the genotypic patterns of 41 protease inhibitor-experienced patients participating in a dose-finding study of tipranavir (BI 1182.2) were analyzed. At the start of the study, all patients had HIV-RNA levels above 5,000 and had failed two previous protease inhibitor-based regimens.

Patients participating in BI 1182.2 initially received the original hard capsule formulation of tipranavir and were later switched to the SEDDS formulation. The first study group of patients received 500 mg tipranavir

BID in combination with 100 mg of ritonavir BID. The second group received 1,000 mg tipranavir BID in combination with 200 mg ritonavir BID.

At baseline, 40/41 (97%) clinical isolates were considered to be susceptible to tipranavir—defined as a less than tenfold increase in IC_{50} —despite decreases in susceptibility to a mean average of 2.9 currently available protease inhibitors. There was no association between the number of protease mutations at baseline and the magnitude of viral load reduction. For example, in the 500 mg tipranavir group, individuals with < 5 baseline protease mutations experienced reductions in viral load of -2.39 log at week 48, compared to a reduction of -2.24 in patients with >5 protease mutations at baseline. Decreased tipranavir susceptibility was associated with a mean of 16 mutations including two or three universal protease inhibitor-associated mutations (UPAMs) at positions V82F/L/T, I84V, and L90M. Five of the six HIV isolates with decreased tipranavir susceptibility had protease mutations at position V82T, and 4/6 had either L33I, V, or F.

Investigators have also looked at baseline phenotypic sensitivity to tipranavir in patients with multiple protease inhibitor experience (Cooper, 2003). In a recent phase IIa dose-optimization study of tipranavir (BI 1182.52), patients who had tried at least two protease inhibitors in the past and had strains of HIV harboring at least one UPAM were randomized to receive one of three tipranavir doses in combination with ritonavir. 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.

Atazanavir

BRISTOL-MYERS SQUIBB'S ATAZANAVIR (BMS-232,632) IS A SEMI-SYMMETRICAL azapeptide agent with an IC_{50} of 2.6 to 5.3 nM, thus more potent *in vitro* than the currently approved protease inhibitors. In dose-ranging studies involving HIV-negative volunteers, single doses of 100 mg up to 1,200 mg appeared to be well tolerated (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 IC_{50} for more than 24 hours. Based on these results, a dose of 400 mg—two 200 mg tablets once a day with food—is being employed in phase III clinical trials. The manufacturer has submitted its new drug application (NDA) in support of atazanavir's approval to the FDA, and a decision from the agency is expected in June.

Atazanavir has had an optimistic showing in clinical trials reported to date. For starters, there have been a number of reports 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 in-

hibitors. 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 (Cahn, 2001; Squires, 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, 2002). Eight hundred antiretroviral-naive 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 log 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 [see Figure 3]. Employing the more sensitive viral load assay, it was determined that only 32% of patients in the atazanavir group and 37% of patients in the efavirenz group had HIV-RNA levels below 50 copies/mL. Differences observed using either the 400 or 50 copies/mL cutoff variables were not statistically significant.

There has been some consternation surrounding these study results. Neither of the study groups performed as well as hoped, and there have been lingering questions as to why the efavirenz group failed to perform better than it did. After all, in DMP266-006, Dupont Pharmaceuticals' pivotal clinical trial pitting efavirenz/zidovudine/lamivudine against indinavir/zidovudine/lamivudine in antiretroviral-naive patients, 67% of patients in the efavirenz group had HIV-RNA levels below 50 copies/mL after 48 weeks of treatment. What possibly could account for the disparities between efavirenz's stellar showing in Dupont's 006 study and lackluster results in BMS's 034 study?

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 excluded from the intent-to-treat analysis. Unfortunately, an intent-to-treat analysis excluding these two criteria has not yet been presented.

Important data regarding atazanavir's resistance profile were reported at the XI International HIV Drug Resistance Workshop, held in July 2002 in Seville, and at the 10th CROI in Boston (Colonno, 2002; 2003). In the Seville presentation, 76 isolates were obtained from atazanavir-treated patients, and 17 had evidence of resistance to the drug. Nine of the 17 isolates were taken from patients who were treatment-naive prior to receiving atazanavir. Eight of these nine atazanavir-resistant isolates harbored an 150L mutation—a unique mutation that may actually increase susceptibility to other protease inhibitors. And in the Boston presentation, in a study of more than 1,500 patients treated in two phase II and three phase III studies, 26 resistant isolates were obtained—all of which harbored

the 150L 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 patients in clinical trials who received atazanavir and saquinavir, the 184V mutation has been documented, which is associated with broad cross-resistance to other protease inhibitors.

TMC114

MUCH LIKE ITS NNRTI CONTENDER TMC 125 (DISCUSSED ABOVE), Tibotec dubs TMC114—its lead protease inhibitor candidate—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.

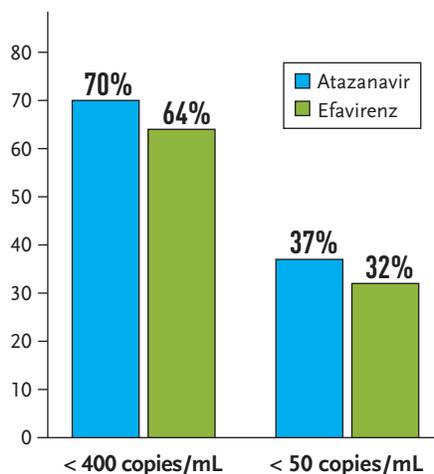
A dose-escalating study of TMC114 has been conducted (Van der Geest, 2001). Two groups of nine HIV-negative volunteers (six active, three placebo) received alternating doses of 100 mg, 200 mg, 400 mg, 800 mg, 1,200 mg, or 1,600 mg. Because the maximum tolerated dose was not reached, an additional panel 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 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 IC₅₀s 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 3200 mg TMC114 dose.

In a phase IIa clinical trial reported at the 10th 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 (Arasteh, 2003). At base-

line, patients 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 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 1.23 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.

Figure 3. **BMS-034: Virologic Effectiveness at 48 Weeks**



Source: Squires, 2002

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 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 fusion and entry process begins with 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, allowing 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 enters the CD4+ cell's membrane. From there, two heptad repeat sequences (HR1 and HR2) of gp41 interact, 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 fusion and entry—the binding of gp120 to CD4, the binding of gp120 to either CCR5 or CXCR4, and the formation of gp41 fusion determinants that allows the virus to mesh 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.

Enfuvirtide (Fuzeon)

FURTHEST ALONG IN DEVELOPMENT ARE THE fusion inhibitors—compounds that block infection by preventing HIV from fusing with and inserting its genetic machinery into host cells. Enfuvirtide (Fuzeon), developed by

Trimeris and Hoffmann-LaRoche, was approved by the U.S. Food and Drug Administration on March 13, 2003, and will be available on a limited basis by the end of the month. The dose is a 90 mg subcutaneous injection administered twice a day.

A detailed review of enfuvirtide, formerly identified as T-20, appears in an article focusing specifically on fusion and entry inhibitors in the June 2002 issue of *The PRN Notebook*.

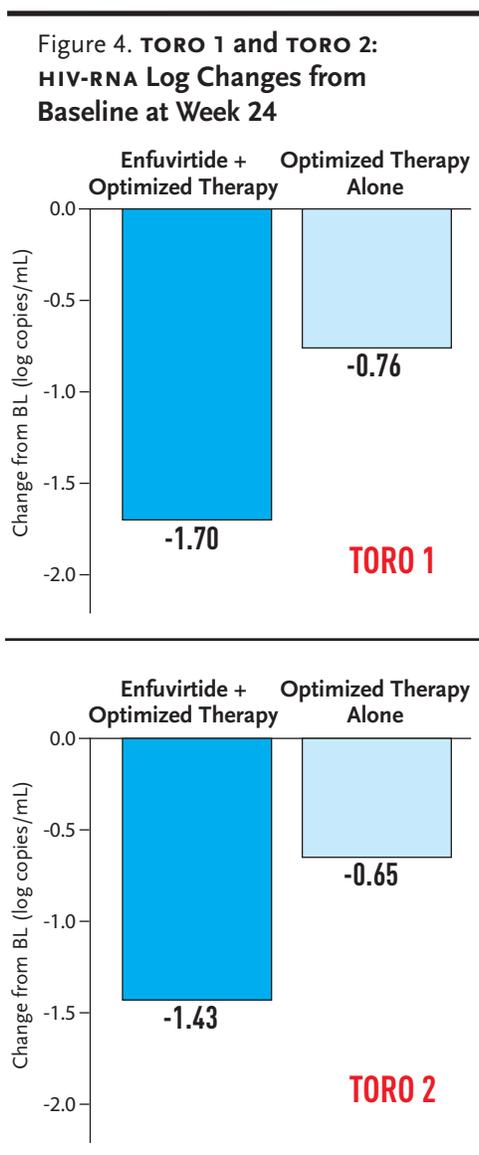
Discussed by Dr. Hammer were the results of TORO 1 and TORO 2—with TORO standing for T-20 vs. Optimized Regimen Only—two pivotal phase III clinical trials being conducted by Trimeris and Roche. Both studies are randomized, open-label trials that enrolled patients at 112 centers worldwide. Patients in the trials were treatment-experienced and/or had documented resistance to each of the three classes of available antiretrovirals. In addition, each patient was required to have HIV-RNA levels greater than 5,000 copies/mL. At entry, an optimized background regimen—consisting of three to five drugs, including up to two newly approved or investigational drugs, if appropriate—was chosen for each patient based on treatment history and antiretroviral resistance testing. After selection of the regimen, patients were randomized 2:1 to receive either the regimen in combination with enfuvirtide or the regimen alone.

TORO 1 enrolled 491 patients who had previously been treated with an average of 12 antiretrovirals. The median baseline viral load was 5.2 log and the median CD4+ count was 80 cells/mm³ (Henry, 2002). TORO 2 enrolled 504 patients who had previously been treated with an average of 11 antiretrovirals (Clotet, 2002). The median baseline viral load was 5.1 log and the median CD4+ count was 98 cells/mm³.

In TORO 1, conducted in North America and Brazil, 37% of patients who were treated with enfuvirtide in combination with an optimized background regimen had HIV-RNA levels below 400 copies/mL at 24 weeks, compared to 16% who received an optimized background regimen alone. Combination therapy with enfuvirtide further reduced HIV-RNA levels to less than 50 copies/mL in 20% of patients, compared to 7% of those who took combination therapy alone.

Patients who received enfuvirtide as part of their combination regimen achieved a mean reduction in HIV-RNA of 1.70 log, compared to 0.76 log among those in the control arm [see Figure 4]. Furthermore, 52% of patients receiving enfuvirtide experienced a 1.0 log or greater reduction in HIV-RNA, compared to 29% who did not receive enfuvirtide. Patients in the enfuvirtide arm experienced a mean CD4+ count increase of 76 cells/mm³, compared to 32 cells/mm³ in the control arm.

Results from TORO 2, the second phase III clinical trial, conducted in Europe and Australia, were consistent with findings from TORO 1. In TORO 2, 28% of patients who were treated with enfuvirtide in combination with an optimized background regimen had HIV-RNA levels below 400 copies/mL after 24



Source: Henry, 2002; Clotet, 2002

weeks, compared to 14% receiving an optimized background regimen alone. Combination therapy with enfuvirtide further reduced viral load to less than 50 copies/mL in 12% of patients as compared to 5% who took combination therapy alone.

The mean difference in the magnitude of decrease in HIV between the two arms at 24 weeks was 0.78 log. Patients who received enfuvirtide as part of their combination regimen achieved a mean reduction in HIV levels of 1.43 log, compared to a mean of 0.65 log for those in the control arm [see Figure 4]. Furthermore, 43% of patients receiving enfuvirtide experienced a 1.0 log or greater reduction in HIV levels, compared to 21% who did not receive enfuvirtide. Patients in the enfuvirtide arm experienced a mean CD4+ count increase of 65 cells/mm³, compared to 38 cells/mm³ in the control arm.

Both *in vitro* and *in vivo* data indicate that HIV resistance to enfuvirtide can and does occur. HIV variants with decreased sensitivity to enfuvirtide contain mutations in the HR1 region of the gp41 complex. The most significant mutations are those found in the GIVQQNNLL sequence, located near the N-terminus of the HR1 region (most notably amino acid positions 36 through 45, the key enfuvirtide binding area). Dr. Hammer pointed out that substitutions associated with decreased enfuvirtide sensitivity may confer reduced viral fitness, a finding that has not yet been explored in clinical trials.

T-1249

T-1249, ANOTHER COMPOUND BEING DEVELOPED BY ROCHE AND TRIMERIS is the second HR-2 peptide analogue fusion inhibitor to enter clinical trials. This molecule, a 39 amino acid peptide, has *in vitro* activity against HIV strains resistant to both standard antiretrovirals and variants resistant to enfuvirtide.

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 µg/ml, which is higher than the target concentration needed to maintain antiviral activity.

A phase I/II clinical trial of T-1249 was conducted in treatment-experienced adults who received no other HIV therapy over the 14-day treatment period (Greenberg, 2002). In this study (T1249-101), patients received T-1249 as monotherapy for 14 days at doses ranging from 6.25 mg/day to 200 mg/day on a once- or twice-daily regimen. The results indicated that T-1249 was well tolerated over 14 days and conferred dose-related suppression of HIV. On day 14, the median decrease in HIV-RNA levels from baseline ranged from 0.10 log for the 6.25 mg/day dose to a 2.0 log reduction in viral copies/mL for the 200 mg/day dose.

In a late-breaking study reported at the 10th CROI, Dr. G. Diego Miralles of Duke University and his colleagues enrolled 54 patients who were failing their enfuvirtide-based regimens while participating in TORO 1 or TORO 2 (reviewed above) (Miralles, 2003). The patients in this study stopped their enfuvirtide and received a ten-day course of T-1249 therapy at a dose of 192 mg/day, which was used in combination with the optimized antiretroviral regimens selected at the beginning of both TORO studies.

Data were available for 25 patients who had completed the study. Prior to switching to T-1249, the median length of T-20 exposure among these patients was 70 weeks and the median time from the onset of enfuvirtide failure was 60 weeks. Twenty-four of the 25 evaluable patients had either genotypic or phenotypic resistance data at baseline, and all 24 had gp41 substitutions associated with enfuvirtide resistance.

On day 11 of the study, the median HIV-RNA decrease was 1.12 log copies/mL and 63% had achieved a viral load reduction of at least 1 log

copies/mL. Also of interest were data linking the effectiveness of T-1249 to the length of prior enfuvirtide therapy: Patients who had been failing enfuvirtide for less than 48 weeks experienced a 1.6 log copies/mL reduction in HIV-RNA, whereas those who had been failing enfuvirtide for longer than 48 weeks experienced only a 0.94 log copies/mL reduction in HIV-RNA upon switching to T-1249.

PRO 542

THERE IS ALSO PROGENICS PHARMACEUTICALS' PRO 542, ALSO KNOWN AS CD4-IgG2. PRO 542 is 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 that can be synthesized using monoclonal antibody technology.

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. 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 peak 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.

A second set of phase II clinical trials, which are also being conducted in adults and children, were kicked off in 2000. 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-C

DR. HAMMER SPENT SOME TIME DISCUSSING THE ORALLY BIOAVAILABLE CCR5 antagonist Schering C (SCH-C), which is being developed by Schering-Plough Research Institute. 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*.

A detailed overview of preclinical data surrounding SCH-C is reviewed in the June 2002 issue of *The PRN Notebook* referenced above. In short, SCH-C is an oxime-piperidine compound that, according to several *in vitro* evaluations, is a bona fide antagonist of CCR5 receptor binding and signal transduction. *In vitro* observations also suggest that SCH-C is CCR5-exclusive—it has no effect on infection of 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. While the pharmacokinetics of SCH-C varied, depending on the dose administered, plasma levels were above the IC₉₀ for most of the dos-

es employed. Twenty-four hours after SCH-C was administered, the drug's C_{\min} was still above the IC_{90} , suggesting that once-daily dosing is possible.

However, there has been some concern regarding QT prolongation seen in the individuals receiving the highest dose of SCH-C. According to data released by Schering-Plough, the mean maximal increase in the QT interval, among individuals who received the 600 mg dose, was 60 msec. There were no symptomatic events (e.g., arrhythmias), although more extensive follow-up testing (e.g., Holter monitoring) was generally not conducted. These observations led the U.S. Food and Drug Administration 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. Dr. Hammer reviewed data from a clinical trial in which 12 patients received SCH-C 25 mg BID and 12 patients received 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 mild headaches and altered taste. Some QT prolongation was observed—the mean increase was 11.5 msec after ten days of treatment.

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, 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 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-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). And 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 reported in Barcelona, 18 HIV-negative study volunteers received single doses of S-1360 (Fujiwara, 2002). In all 18 patients, the C_{\max} 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, involving HIV-positive patients, are now under way.

There are also the naphthyridine carboxamides, which include Merck's contenders L-870,812 and L-870,810 (Hazuda, 2002). These two com-

pounds have potent antiretroviral activity *in vitro*—the IC_{95} for L-870,812 was 0.250 mM and the IC_{95} 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).

VI. Zinc Finger Inhibitors

HIV ZINC FINGERS ARE HIGHLY CONSERVED MOTIFS THAT ARE CHARACTERIZED by the amino acid sequence C-X-C-X-H-X-C (C=cysteine; H=histidine; X=any amino acid), in which C and H act as chelating residues for zinc. These motifs are found in the HIV nucleocapsid protein, which as a precursor polyprotein is crucial for both early and late stages of viral replication. Zinc finger inhibitors electrophilically attack the sulfur atoms in the cysteine residues, which leads to zinc ejection and incapacitation of this 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.

VII. RNA Interference

IT ALL BEGAN LESS THAN TEN YEARS AGO, WHEN A TEAM OF RESEARCHERS under the direction of Dr. Rich Jorgensen, who is currently an associate professor in the Department of Plant Sciences at the University of Arizona, was experimenting with petunias (Jorgensen, 1996). Dr. Jorgensen's group was attempting to deepen the color of these household plants with the use of a pigment-producing gene. However, upon injecting the plants with the gene, the flowers actually lightened considerably, turning white in some cases. After some sleuthing, Dr. Jorgensen's team suggested that what was being seen was “cosuppression”—the suppression of both the homologous endogenous gene and the introduced pigment-producing gene.

Additional studies conducted over the years have found that this is not simply a phenomenon related to petunias. Gene expression silencing can occur in a variety of plants, nematodes, drosophila, and mammals and occurs when short double-stranded segments of RNA (siRNA)—sometimes referred to as “guide RNAs”—are introduced and bind to specific locations of host messenger RNA (mRNA) by complementary base pairing. It is currently believed that siRNAs are produced when the enzyme Dicer—a member of the RNase III family of double-stranded RNA (dsRNA)-specific ribonucleases—cleaves dsRNA, which can be introduced directly or via a transgene or virus. What's left are de-

graded siRNAs that are usually between 19 and 25 nucleotides long, which can target and inhibit the expression of virtually any genes.

Since discovering that RNA interference works in human cells, various research teams have been working to develop silencing techniques to inhibit HIV replication. And there are two possible areas of development to consider: the silencing of genes responsible for the expression of key receptors and coreceptors on uninfected cells, and the interference of genes responsible for the replication of HIV inside infected cells.

RNA interference (RNAi) as a potential HIV therapeutic has been gaining a great deal of attention in recent years. In fact, there wasn't an empty seat in the house during an afternoon symposium focusing specifically on RNA interference at the 10th CROI. One research team described efforts to insert siRNAs for HIV envelope sequences into specific cells (Rossi, 2003). This resulted in a potent inhibition of HIV gene expression following coinfection with HIV in both cultured and primary cells. And in another study in which macrophages were transfected with siRNA, there was significant suppression of HIV replication, including strains resistant to approved antiretroviral drugs (Lieberman, 2003).

While it might be some time before RNAi is ready to enter clinical trials, the various proof-of-concept research currently under way indicates that the future of gene therapy is ripe with potential.

Conclusion

IN SUMMARY, DR. HAMMER STRESSED THAT THERE IS AN URGENT NEED to continue developing compounds that are unique, particularly with respect to their resistance profiles, and that a number of promising candidates are in development in both existing classes and new classes. Clinical development of any new drug is a challenge, but a continued sense of cautious optimism that the therapeutic options will meaningfully expand is warranted.



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