

New Drugs for the Treatment-Experienced Patient

Joseph Eron, MD

Associate Professor of Medicine and Director, Clinical Core UNC Center for AIDS Research, University of North Carolina at Chapel Hill

SUMMARY BY TIM HORN

EDITED BY JAY DOBKIN, MD; MICHAEL SAAG, MD

TREATMENT OPTIONS FOR ANTIRETROVIRAL-experienced patients leave a lot to be desired. According to Dr. Joe Eron, patients who have treatment experience in all three classes of currently available antiretrovirals have, at best, a 30% chance of reducing their viral load to levels below 400 copies/mL upon initiating a salvage regimen. Cross-resistance within each class of drugs, particularly the protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), essentially hobbles the effectiveness of switching therapies in the face of virologic failure.

It goes without saying that new antiretrovirals are definitely needed—drugs that have potent and durable efficacy profiles for patients with both limited and extensive antiretroviral experience.

For the sake of tailoring his talk to focus exclusively on new drugs in development for antiretroviral-experienced patients, Dr. Eron excluded several compounds in development. Among these were the nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine (FTC); the NNRTI emivirine (MKC-442); and the protease inhibitors DMP-450 and GW-433908, an amprenavir (Agenerase) prodrug. “These drugs are all very similar to compounds we now currently have,” explained Dr. Eron. “While each drug may have an advantage over current drugs, these benefits, which include better dosing schedules, will likely be enjoyed only by antiretroviral-naïve patients. Fortunately, there are still quite a few drugs left to discuss, many of which stand to help those who need them most.”

I. New Nucleoside/ Nucleotide Analogues

Diaminopurine Dioxalane (DAPD)

DAPD IS BEING DEVELOPED BY TRIANGLE Pharmaceuticals. It is a novel dioxalane purine NRTI that is rapidly converted in

humans by adenosine deaminase into D-dioxolane guanine (DXG), a metabolite that has potent activity against HIV and HBV.

According to *in vitro* data presented at the 3rd International Workshop on HIV Drug Resistance and Treatment Strategies, held in June 1999, DAPD was found to inhibit wild-type and mutant isolates resistant to AZT (Retrovir) and 3TC (Borrito-Esoda, 1999). The drug was also reported to be active against strains collected from patients who have failed various NRTI and NNRTI combination therapies, including those with variants harboring the multi-NRTI-resistant mutations Q151M and T69SS.

As for its own resistance profile, *in vitro* data indicate that DAPD selects for the L74V and K65R mutations that are associated with fourfold and eightfold increases in the drug's IC₅₀, respectively. These mutations may confer at least some cross-resistance to dDI and ddC.

More recently, in a pilot study conducted by Dr. Steven Deeks and his colleagues, 20 treatment-experienced patients received oral doses of 200 mg, 300 mg, or 500 mg twice daily of DAPD monotherapy (Deeks, 2000). All patients had previously failed an average of seven antiretroviral drugs and had been treated for an average of four years. After 15 days of therapy, the reduction in HIV-RNA ranged from 0.5 to 1.1 log. Data correlating genotype or phenotype to virologic response to DAPD were not presented by Dr. Deeks. All doses were generally well tolerated, and the pharmacokinetics data generated thus far may support a once-daily dosing schedule.

Tenofovir Disoproxil Fumarate (Bis [POC] PMPA; GS-902)

TENOFOVIR DF IS GILEAD SCIENCE'S SECOND adenosine nucleotide analogue and is an oral prodrug of PMPA. *In vitro*, it has potent activity against HIV, SIV and Moloney-murine sarcoma virus at doses several hundred times less than those toxic to cells. Preliminary data presented by Dr. Steven

Deeks and his colleagues in 1998 demonstrated a 1 log reduction in HIV-RNA in HIV-infected patients—more than 50% of whom were treatment-experienced—who received tenofovir DF 300 mg once daily as monotherapy for 28 days (Deeks, 1998).

According to *in vitro* data presented by Gilead's Dr. Michael Miller at the recent 4th International Resistance Workshop, the resistance pattern for tenofovir DF is similar to that of its chemical predecessor adefovir, a compound no longer in development for the treatment of HIV (Miller, 2000). Low-level resistance to tenofovir DF is mediated by the K65R mutation. Of particular interest, though, is the finding that the M184V mutation associated with 3TC resistance may increase HIV sensitivity to the drug. HIV harboring the multi-NRTI-resistance mutation Q151M remained susceptible to tenofovir DF, but mutations at codon position T69SS—which can also induce high-level cross-class resistance—were associated with decreased tenofovir DF sensitivity.

At the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) last fall in San Francisco, Dr. Robert Schooley presented preliminary 24-week data from a placebo-controlled study comparing three doses of tenofovir DF—75 mg, 150 mg, and 300 mg given once daily—added to a stable, yet failing anti-

Chemical Name: DAPD

Generic Name: N/A

Brand Name: N/A

Sponsor: Triangle Pharmaceuticals

Dosing: Twice daily in early studies; once-daily dosing possible.

Development Phase: Phase I/II

Resistance Profile: Selects for the L74V and K65R (*in vitro*); may confer some cross-resistance to dDI and ddC; appears active against variants with Q151M and T69SS mutations (*in vitro*).

Safety Profile: “Generally well tolerated” in pilot study (Deeks, 2000).

Chemical Name: Bis(POC) PMPA
Generic Name: Tenofovir
Brand Name: N/A
Sponsor: Gilead Sciences
Dosing: 300 mg once daily
Development Phase: Phase II
Resistance Profile: Selects for the K65R mutation (<i>in vitro</i>); may confer some cross-resistance with ddI and ddC; variants with M184V appear hypersensitive to tenofovir; tenofovir active against variants with Q151M mutation; variants with T69SS mutation less sensitive to tenofovir.
Safety Profile: "No serious toxicities;" no nephrotoxicity reported (Schooley, 1999).

retroviral regimen (Schooley, 1999). Most patients enrolled in the study had been receiving antiretroviral therapy for at least four years and a significant percentage—almost 94%—carried variants resistant to AZT, 3TC, or both; more than 60% had mutant HIV conferring resistance to at least one protease inhibitor. At the 300 mg dose, HIV-RNA decreased by approximately 0.75 log, a benefit that proved durable for at least 24 weeks. Of note, no serious toxicities were reported; nephrotoxicity similar to that seen in patients receiving adefovir was not observed in this study of patients receiving tenofovir DF.

"The data from this study really look promising," commented Dr. Eron. "But, for the sake of fairness, we really need to see some more efficacy and side effect data before we can say that tenofovir DF is a sure thing."

II. New Non-Nucleoside Reverse Transcriptase Inhibitors

Capravirine (AG-1549)

ONE OF THE MORE PROMISING NNRTIS DISCUSSED by Dr. Eron was capravirine (AG-1549). According to Agouron Pharmaceuticals, the manufacturer of the compound, AG-1549 is active against HIV isolates that contain *single* 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 dose of capravirine will likely be 1400 mg taken twice daily, based on positive results using this and a lower dose in a recent 10-day clinical trial; 1400 mg bid was associated with a >1 log drop in antiretroviral-naïve patients (Hernandez, 2000). "This may seem like a large dose," Dr. Eron explained to a number of raised eyebrows in the room. "However, Agouron is currently developing the drug using 700 mg tablets, which translates into two pills twice a day." With respect to actual data in antiretroviral-experienced patients, Dr. Eron noted that, "phase III studies looking at this drug in experienced patients are expected to begin enrollment soon. We haven't seen much of anything yet, but this is certainly one to watch."

DPC-961

DPC-961 IS A NEW NNRTI BEING DEVELOPED by DuPont Pharmaceuticals. According to the manufacturer, the half-life of DPC-961 is a whopping 140 hours, a finding that will lead to a most favorable dosing schedule. The drug also has three- to eightfold greater potency against K103N-containing isolates and robust activity against variants with single substitutions such as Y181C and V106A.

"Development of DPC-961 has slowed down," commented Dr. Eron. "We're not exactly sure what's going on, and this is not to say the drug will not eventually move forward, but trials may begin enrolling soon."

III. Protease Inhibitors

Lopinavir (Kaletra; ABT-378/r)

IN VITRO, LOPINAVIR (ABT-378/R)—A PEPTIDOMIMETIC protease inhibitor in development by Abbott Laboratories—is approximately 10 times more powerful than its first-generation sibling ritonavir (Norvir). When used with small amounts of ritonavir—hence, the little "r" in its name—lopinavir's bioavailability is considerably prolonged, allowing a twice-daily dosing schedule and enhanced efficacy. One Kaletra capsule contains 133 mg of lopinavir and 33 mg of ritonavir, and the recommended daily dose is three capsules taken twice a day with food. The Food and Drug Administration (FDA) is currently evaluating the drug, and it is expected to be approved this fall. [Editor's note: A brief discussion of lopinavir's safe-

ty and efficacy in antiretroviral-naïve patients can be found in "Treatment Strategies for the Antiretroviral-Naïve Patient," beginning on page 4].

In terms of its resistance profile, lopinavir was specifically developed to be active against isolates that contain mutations at position v82 of the protease enzyme. A substitution at position v82 is known to be a primary mutation associated with resistance to ritonavir, indinavir, and possibly saquinavir. Other mutations, including M46I/L (a primary mutation associated with indinavir resistance) and 184V (a secondary mutation reported among all currently available protease inhibitors) can be selected by *in vitro* passage of virus in the presence of the drug (Mo, 1999).

Seventy-two week data from Abbott's M97-765 study—a trial evaluating lopinavir in patients who had failed one protease inhibitor-based regimen—were presented at the 13th International AIDS Conference (Thompson, 2000). A quick glimpse at the 72-week data is provided in Figure 1.

In the study, 70 patients were treated with lopinavir monotherapy for two weeks; nevirapine (Viramune) and at least one NRTI were then added to complete the new regimen. Approximately two-thirds of all patients had a greater than fourfold decrease in susceptibility to one currently available protease inhibitor, most notably the PI taken prior to enrollment in the lopinavir study; one-third of the patients had a greater than fourfold decrease in susceptibility to three currently available PIs. The proportion of patients maintaining an undetectable viral load after 72 weeks of therapy was 88% using the the <400 copies/mL cutoff and 73% using the <50 copies/mL cutoff. It is important to note,

Chemical Name: AG-1549
Generic Name: Capravirine
Brand Name: N/A
Sponsor: Agouron Pharmaceuticals
Dosing: 1400 mg twice daily (2 700 mg tablets BID)
Development Phase: Phase II
Resistance Profile: Active against variants with single key NNRTI mutations (K103N, V106A, and L100I); dual key mutations decreases sensitivity to capravirine.
Safety Profile: "Generally well tolerated" in 10-day study (Hernandez, 2000).

Chemical Name: ABT-378/r
Generic Name: Lopinavir
Brand Name: Kaletra
Sponsor: Abbott Pharmaceuticals
Dosing: Lopinavir/ritonavir coformulation (400 mg/100 mg twice daily); three capsules BID.
Development Phase: Under FDA review; Phase III ongoing; expanded access program (1-888-711-7193)
Resistance Profile: Active against variants with mutation at position v82 (associated with ritonavir and indinavir resistance); selects for M46I/L and I84V mutations in HIV protease; favorable PK and IC50 against PI-resistant variants.
Safety Profile: Diarrhea, nausea, headache, elevated LFTs and lipids (Kessler, 2000).

however, that all single-PI-experienced patients entering this study were naive to NNRTI therapy. Dr. Eron asserted that, "even for patients with a single PI failure, these results were quite good when compared to many of the other studies that we've seen. A plausible explanation for the results we're seeing can be attributed to the pharmacokinetic properties of ABT-378 being combined with ritonavir. Concentrations of ABT-378 *in vivo* are significantly higher than those needed to suppress wild-type and drug-resistant variants *in vitro* by 50%, 90%, or even 99%."

As for the 72-week safety data, reported in a separate presentation at the Durban conference, the most common adverse events in M97-765 were diarrhea (approx-

mately 23%), nausea, asthenia, and headache (Kessler, 2000). With respect to laboratory values, 12 patients experienced elevations in their liver function tests. Triglyceride and cholesterol levels increased, on average, by 150 mg/dL and 30 mg/dL, respectively. Three patients discontinued this study because of adverse events; 12/70 (17%) discontinued the regimen altogether.

Preliminary results from a lopinavir study enrolling patients with a history of multiple PI failures were also presented at the 13th International AIDS Conference (Clumek, 2000). A total of 57 patients were enrolled in the study, all of whom were naive to NNRTI therapy and had been treated, on average, with three PIs in the past (68% had a greater than fourfold decrease in susceptibility to three or more PIs). Interestingly, *in vitro* data presented showed that most patients enrolling in this study harbored variants with high-level resistance to lopinavir (Kempf, 2000).

All patients were treated with one of two offered doses of lopinavir: 400 mg (with 100 mg ritonavir) or 533 mg (with 133 mg ritonavir). Lopinavir was combined with efavirenz (Sustiva) and two NRTIs. After 24 weeks of therapy, approximately 80% of patients receiving the lower-dose lopinavir regimen and 96% receiving the higher-dose lopinavir regimen had HIV-RNA levels below 400 copies/mL. Despite the fact that all patients were NNRTI-naive and likely benefited from the addition of efavirenz, it's important to note that many patients had baseline resistance to three or more of the currently available NRTIs. In other words, without the benefit of lopinavir, efavirenz would have offered nothing more than a short-lived monotherapy advantage.

Responses to therapy in patients with multiple PI experience appear to be associated with baseline phenotypic profiles. According to an analysis presented at the 4th International Resistance Workshop, *in vitro* resistance data were reported (Colonno, 2000). Using phenotypic resistance assays, 63 HIV isolates were exposed to varying concentrations of BMS-232,632 in an effort to learn more about the drug's activity against variants harboring mutations conferring resistance to currently available PIs. According to the report, variants with low- to intermediate-level resistance (less than fivefold decrease in sensitivity) to one or two PIs were still sensitive to BMS-232,632. Isolates with intermediate- to high-level resistance (greater than fivefold decrease in sensitivity) to three or more currently available PIs showed some loss of sensitivity to the drug, although 70% were still clearly susceptible.

copies/mL) *in vivo* after 24 weeks of therapy (Kempf, 2000a). Among patients harboring variants with decreased lopinavir sensitivity between 10-fold and 20-fold, approximately 78% achieved undetectable HIV-RNA levels after 24 weeks. Once *in vitro* lopinavir sensitivity decreases more than 40-fold, the expectancy that patients will either achieve or maintain an undetectable viral load decreases to less than 50%.

BMS-232,632

BRISTOL-MYERS SQUIBB'S BMS-232,632 IS A semi-symmetrical azapeptide agent with an IC50 of 2-5nM, thus more potent than the currently approved protease inhibitors. Selected mutations during *in vitro* passage experiments include those at positions N88, M46, A71 and I84, all of which overlap with approved protease inhibitors. Some cross-resistance to approved protease inhibitors was noted in virus selected by BMS-232,632. Similarly, resistant virus selected by approved agents in some cases demonstrated six- to ninefold losses of sensitivity to BMS-232,632 (Gong, 1999).

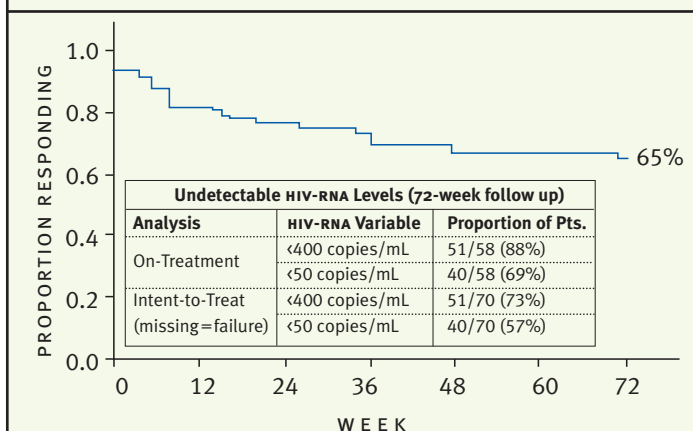
Pharmacokinetic studies of BMS-232,632 support its use as a once-daily protease inhibitor. However, the actual dose has not yet been correctly determined. The drug will likely need to be taken with food.

In antiretroviral-naive patients, combining the drug with d4T (Zerit) and the new once-daily formulation of ddI (Videx) was associated with a 2.0 to 2.5 log reduction in HIV-RNA after 16 weeks of therapy (Sanne, 2000). In terms of side effects, increased bilirubin levels occurred in more than half of the patients enrolled.

At the 4th International Resistance Workshop, *in vitro* resistance data were reported (Colonno, 2000). Using phenotypic resistance assays, 63 HIV isolates were exposed to varying concentrations of BMS-232,632 in an effort to learn more about the drug's activity against variants harboring mutations conferring resistance to currently available PIs. According to the report, variants with low- to intermediate-level resistance (less than fivefold decrease in sensitivity) to one or two PIs were still sensitive to BMS-232,632. Isolates with intermediate- to high-level resistance (greater than fivefold decrease in sensitivity) to three or more currently available PIs showed some loss of sensitivity to the drug, although 70% were still clearly susceptible.

"This drug is now entering phase III

FIGURE 1: Lopinavir in Tx-Experienced Patients: Time to Virologic Failure and 72-Week Data



Source: 13th International AIDS Conference (Thompson, 2000)

studies,” Dr. Eron added. “Again, this is another drug to watch.”

Tipranavir

TIPRANAVIR IS A NONPEPTIDIC DIHYDROXYRONE, a new class of protease inhibitors believed to have greater flexibility in conforming to enzyme variants resistant to current PIs. The compound was originally developed by Pharmacia & Upjohn and was recently licensed to Boehringer Ingelheim.

As with its unique mechanism of action, tipranavir also differs from other currently available protease inhibitors in its metabolism. The drug induces the cytochrome P450 pathway, whereas current protease inhibitors inhibit this enzyme system. In early phase II studies, a whopping 1500 mg of tipranavir, taken three times daily, was required to achieve the necessary trough concentration. To circumvent this hurdle, the manufacturer is currently developing a self-emulsifying drug delivery system (SEDDS) for the compound. Tipranavir will also need to be combined with low doses of ritonavir (100 mg) to reverse the rapid metabolism of the drug by cytochrome P450.

An initial glimpse into the activity of tipranavir against multiple-PI-resistant HIV strains was provided by Dr. Brendan Larder and his colleagues last year at the 3rd International Resistance Workshop in San Bernardino Inn. Studied by Dr. Larder’s team were 107 isolates documented to be highly cross-resistant to three or four protease inhibitors, along with 28 isolates resistant only to individual protease inhibitors. Of the 107 cross-resistant isolates, only three demonstrated a greater than tenfold decrease in sensitivity to tipranavir. Eight of the isolates tested were classified as being moderately resistant to tipranavir, defined as a four- to tenfold decrease in sensitivity to the drug. The remaining 96 isolates were found to be completely susceptible—meaning a less than fourfold decrease in sensitivity—to the drug. Isolates with key dual mutations, such as I84V with either V82A or L90M, were found to be the ones most resistant to tipranavir. Data to support Dr. Larder’s optimistic findings were recently published by an Italian team of investigators in *Antimicrobial Agents and Chemotherapy* (Rusconi, 2000).

A phase II clinical trial involving patients who have failed one PI-based regi-

men in the past is currently under way. Phase II/III studies involving patients with multiple-PI experience have not yet been developed, as Boehringer Ingelheim is waiting on the final development of the SEDDS formulation and correct dosing information prior to moving forward.

IV. New Drug Classes

Fusion Inhibitors: Chemokine Receptor Antagonists and gp41 Binders

PATHOGENESIS-BASED RESEARCH HAS DEMONSTRATED that natural ligands of the CD4+ cell chemokine receptors—which function as coreceptors for HIV—can inhibit HIV replication and that mutations in both chemokine receptor (CCR5; CCR2) and chemokine (SDF-1) genes are associated with slower rates of progression (for a more extensive review, see “The HIV Envelope Glycoproteins: Their Roles in Virus Entry and as a Vaccine Target,” a summary of a PRN lecture delivered by Dr. John Moore, in the March 1999 issue of *The PRN Notebook*).

A number of compounds have been described to have *in vitro* activity as chemokine receptor antagonists. CXCR4 antagonists currently in the early stages of development include AMD 3100 (Johnson Matthey/Anormed Pharmaceuticals), T-22 (Seikagaku Pharmaceuticals), and ALX40C-4C (Allelix Pharmaceuticals). CCR5 antagonists currently being examined—mostly *in vitro* and in animal models—include the natural ligands for CCR5 (e.g., MIP-1 α , MIP-1 β , and RANTES), as well as the analogues AOP-RANTES and TAK-779.

Unfortunately, there are major challenges to the full development of chemokine receptor antagonists as a clinically effective therapeutic option. For example, CCR5 antagonists, which may prevent cellular infection by macrophage-tropic HIV strains, may push the virus to become a more aggressive T-tropic variant. Another concern is human pathology. While it’s not likely that CCR5 deletion would result in any negative biological or physiological consequences, major developmental effects were seen in CXCR4-knockout mice, including vascular system problems and embryonic death.

CCR5 and CXCR4 antagonists continue to move through the pipeline slowly and cautiously. However, new data involving pentafuside—a drug that targets the HIV

glycoprotein gp41 and does not directly interfere with CCR5+ cells—continue to be made available.

Pentafuside (T-20)

PENTAFUSIDE (T-20) IS BEING DEVELOPED BY Hoffmann-LaRoche and Trimeris, Inc. A preliminary report by J.M. Kilby and colleagues indicated that pentafuside is capable of acutely reducing HIV-RNA levels to an extent—1.96 log reduction over a 14-day period—similar to protease inhibitor-containing therapies (Kilby, 1998).

Data are available from a phase II, randomized, open-label study of the drug in heavily pretreated patients (Lalezari, 1999). Seventy-eight patients with a median HIV-RNA titer of 100,000 copies/mL and a mean CD4+ count of 117 cells/mm³ were assigned to six groups representing pentafuside doses ranging from 12.5 to 22 mg/day. Because pentafuside is a peptide, it cannot be administered orally. Thus, patients enrolled in this study received therapy by one of two routes: continuous intravenous infusion via an automatic pump or twice-daily subcutaneous injections.

The drug was well tolerated at all doses throughout the 28-day treatment period. Sustained steady-state plasma concentrations of pentafuside were observed for both delivery methods, suggesting that twice-daily self-injections—a considerably more favorable option for many patients—can be developed further. The average maximum change from baseline ranged from -0.3 to -1.6 log across the treatment groups. The magnitude and durability of viral load suppression was greater in patients with baseline viral load <100,000 copies/mL.

Chemical Name: PNU-140690

Generic Name: Tipranavir

Brand Name: N/A

Sponsor: Boehringer Ingelheim (formerly Pharmacia & Upjohn)

Dosing: New formulation (SEDDS) in development; will be combined with low doses of ritonavir.

Development Phase: Phase II/III

Resistance Profile: Active against variants with high-level resistance to current PIs (*in vitro*).

Safety Profile: N/A with respect to new formulation.

Chemical Name: T-20
Generic Name: Pentafuside
Brand Name: N/A
Sponsor: Hoffmann-LaRoche and Trimeris, Inc.
Dosing: subcutaneous injections twice daily.
Development Phase: Phase III
Profile: Novel therapeutic; active against variants resistant to all current antiretrovirals; gp41 resistance to pentafuside documented.
Safety Profile: "Well tolerated;" subcutaneous nodules (Cohen, 2000).


New data from study T-20-205, a phase II open-label trial involving patients who had received pentafuside in prior short-term studies, were presented at the 13th International AIDS Conference by Dr. Cal Cohen (Cohen, 2000). Prior to entering the study, patients had failed, on average, 10 antiretrovirals—97% had failed at least one PI and 79% had failed at least one drug in all three currently available classes—and initiated twice-daily 50 mg pentafuside therapy with a viral load of 4.8 log and a CD4+ count of 135 cells/mm³. After 48 weeks of follow-up, only 41/71 (58%) remained on therapy. However, the average HIV-RNA decrease among these patients was 1.5 log. Approximately 39% had HIV-RNA levels below 400 copies/mL, and 22% had HIV-RNA levels below 50 copies/mL.

"The one side effect we're seeing quite a bit of," added Dr. Eron, "are subcutaneous nodules forming at the site of the injection. Trimeris and Hoffmann-LaRoche are currently developing a new formulation, although injections are still very much likely."

T-1249, Trimeris' second gp41 inhibitor, is active against HIV-1, HIV-2, and SIV. In primates, it has a longer half-life than pentafuside—its AUC is twofold greater—which may allow for once-daily or, perhaps, a once-every-other-day dosing schedule. "Some data suggest that T-1249 is more potent than pentafuside and active against pentafuside-resistant isolates," Dr. Eron said.

Conclusion

IN SUMMATION, DR. ERON STRESSED THAT, even though a handful of new drugs appear promising for treatment-experienced patients, no drug will have a worthwhile ef-

fect on its own. "We really need to start testing these new drugs in combination with each other," concluded Dr. Eron. "Developing and approving drugs one at a time isn't going to work for multi-drug experienced patients. They'll still need to take a new drug with at least one or two other drugs they've never seen before. This is definitely a factor to consider." 

References

Borroto-Esoda K, Mewshaw J, Wakefield D, et al. **The nucleoside reverse transcriptase inhibitor DAPD is active against resistant HIV-1 isolates from patients failing standard nucleoside therapy** [Abstract 3]. 4th International Workshop on HIV Drug Resistance and Treatment Strategies, Sitges, 2000.

Clumek N, Girard PM, Telenti A, et al. **ABT-378/ritonavir (ABT-378/r) and efavirenz: 16-week safety/efficacy evaluation in multiple PI experienced patients** [Abstract Tu-PeB3196]. XIII International AIDS Conference, Durban, 2000.

Cohen C, Lalezari J, Eron J, et al. **Forty-eight week analysis of patients receiving T-20 as a component of multi-drug salvage therapy** [Abstract LBPeb116]. XIII International AIDS Conference, Durban, 2000.

Deeks S, Kessler H, Eron J, et al. **Short-term monotherapy of DAPD in HIV-infected patients.** 4th International Workshop on HIV Drug Resistance and Treatment Strategies, Sitges, 2000.

Deeks S, Barditch-Crovo P, Lietman PS, et al. **The safety and efficacy of PMPA prodrug monotherapy: Preliminary results of a phase I/II dose-escalation study** [Abstract LB8]. 5th Conference on Retroviruses and Opportunistic Infections, Chicago, 1998.

Gong Y, Robinson B, Rose R, et al. **Resistance profile and drug combination studies of HIV-1 protease inhibitor BMS-232632** [Abstract 603]. 6th Conference on Retroviruses and Opportunistic Infections, Chicago, 1999.

Hernandez J, Amador L, Amantea M, et al. **Short-course monotherapy with AG1549, a novel nonnucleoside reverse transcriptase inhibitor, in antiretroviral naive patients** [Abstract 669]. 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2000.

Kempf D, Isaacson J, King M, et al. **Genotypic correlates of reduced *in vitro* susceptibility to ABT-378 in HIV isolates from patients failing protease inhibitor therapy.** 4th International Workshop on HIV Drug Resistance and Treatment Strategies, Sitges, 2000.

Kempf D, Brun S, Rode R, et al. **Identification of clinically relevant phenotypic and genotypic breakpoints for ABT-378/ritonavir in multiple PI-experienced, NNRTI-naïve patients.** 4th International Workshop on HIV Drug Resistance and Treatment Strategies, Sitges, 2000a.

Kessler H, Eron J, Hicks CB, et al. **Analysis of safety data from ABT-378/ritonavir (ABT-378/r) in two phase II clinical trials** [Abstract TuPeB3198]. XIII International AIDS Conference, Durban, 2000.

Kilby JM, Hopkins S, Venetta TM, et al. **Potent suppression of HIV-1 replication in humans by T-20, a peptide inhibitor of gp41-mediated virus entry.** *Nature Medicine* 1302-1307, 1998.

Leleziari J, Eron J, Carlson M, et al. **Safety, Pharmacokinetics, and Antiviral Activity of T-20 as a Single Agent in Heavily Pre-treated Patients** [Abstract LB-13]. 6th Conference on Retroviruses and Opportunistic Infections, Chicago, 1999.

Mo H, Chernyavski T, Lu L, et al. **Multiple Pathways to Resistance to ABT-378 Observed by *In vitro* Selection** [Abstract 117]. 6th Conference on Retroviruses and Opportunistic Infections, Chicago, 1999.

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.

Rusconi S, La Seta Catamancio S, Citterio P, et al. **Susceptibility to PNU-140690 (tipranavir) of human immunodeficiency virus type 1 isolates derived from patients with multidrug resistance to other protease inhibitors.** *Antimicrob Agents Chemother* 44:1328-32, 2000.

Sanne I, Piliero P, Wood R, et al. **Safety and antiviral efficacy of a once-daily HIV-1 protease inhibitor, BMS232632: preliminary results from a phase II clinical trial** [Abstract 672]. 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2000.

Schooley R, Myers D, Ruane P, et al. **A double-blind, placebo-controlled study of tenofovir disoproxil fumarate (TDF) for the treatment of HIV infection** [Abstract LB-19]. 39th Inter-science Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 1999.

Thompson M, Murphy R, Gulick R, et al. **Analysis of duration of virologic response in two phase II studies of ABT-378/ritonavir (ABT-378/r) at 72 weeks** [Abstract TuPeB3197]. XIII International AIDS Conference, Durban, 2000.