New Drugs for the Treatment-Experienced Patient

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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) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), essentially hobbles the effectiveness of switching therapies in the face of virologic failure.

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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 HCV.

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 (Borotto-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 T69S.

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 adevar, 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 T69S—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-
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 103 and 101 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-naive 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."

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 safety and efficacy in antiretroviral-naive patients can be found in “Treatment Strategies for the Antiretroviral-Naive 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 V82 (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 NNRTI 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 rit 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:** 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 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).

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However, that all single-PI-experienced patients entering this study were naive to the nRTI 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 (approximately 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 the nRTI therapy and had been treated, on average, with three PIIs in the past (68% had a greater than fourfold decrease in susceptibility to three or more PIIs). 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 NNRTIs. 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 ITT-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 NNRTIs. 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 genotypic profiles. According to an analysis presented at the 4th International Resistance Workshop, variants conferring a less than tenfold decrease to lopinavir at baseline were still likely to be pushed to undetectable levels (<400 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 expectation 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 azapeptidase 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 antitetroviral-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 (Colonnio, 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 PIIs. According to the report, variants with low- to intermediate-level resistance (less than fivefold decrease in sensitivity) to one or two PIIs 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 PIIs showed some loss of sensitivity to the drug, although 70% were still clearly susceptible.

“This drug is now entering phase III...
patients who have failed one regimen. However, Larder's optimistic findings were recently challenged as some patients failed to respond to tipranavir. Data to support Dr. Eron's hypothesis that tipranavir will also need to be combined with low doses of ritonavir to reverse the metabolism of the drug by cytochrome P450.

An initial glimpse into the activity of tipranavir against multiple-rt-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 V82M, 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).

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; CXCR4) 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 ALX404C-4C (Allexis Pharmaceuticals). CCR5 antagonists currently being examined—mostly in vitro and in animal models—include the natural ligands for CCR5 (e.g., SDF-1α, MIP-1β, 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 cause 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 (standard) 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 PI (in vitro). |
| Safety Profile: N/A with respect to new formulation. |
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 injection sites 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 half-life 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 effect 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**


