New Anti-HIV Therapies

Compared to previous years, advances in the field of HIV antiviral research today are few and far between. Only a handful of new drugs in development block HIV reproduction by new mechanisms. Most experimental anti-HIV drugs are simply improved versions of existing therapies or new variations of those currently available. Such therapies are likely to offer only incremental benefits in potency, simplified dosing and reduced side effects. Some will claim to be effective against anti-HIV drug resistant viruses based on laboratory tests, but it remains to be seen whether they will help people with highly resistant virus.

This article reviews the new anti-HIV drugs currently, or soon to be, in studies. We also note any attributes about each drug that may make it different (or not) from those currently available.

New Protease Inhibitors

TIPRANAVIR

Study results were presented for tipranavir, a new protease inhibitor being developed by Boehringer Ingelheim. Considerable interest in this drug is driven by data suggesting that it remains active against HIV resistant to most other protease inhibitors. One study compared 1,200mg tipranavir taken twice a day to either 300mg or 1,200mg tipranavir together with 200mg ritonavir taken twice daily. This was only a 14-day study and none of the 31 volunteers had taken anti-HIV therapy before. At study end, there was an average viral load reduction of about 1.5 log (32-fold) among the two groups on tipranavir with ritonavir and about 0.7 log (5-fold) reduction among those taking tipranavir alone. Side effects included diarrhea in all three groups and nausea among those on the high dose tipranavir/ritonavir combination.

A second study involved 41 people who had previously taken multiple regimens that included protease inhibitors but not non-nucleoside reverse transcriptase inhibitors (NNTRIs). At the beginning, participants took twice daily regimens of either 1,200mg tipranavir + 100mg ritonavir or 2,400mg tipranavir + 200mg ritonavir. They also received the NNRTI efavirenz and one new nucleoside reverse transcriptase inhibitor (NRTI). During the study a new formula of tipranavir was developed and people on the 1,200mg and 2,400mg doses were changed to 500mg and 1,000mg of the new formula respectively.

Tipranavir as a Second Line Therapy

<table>
<thead>
<tr>
<th>Tipranavir</th>
<th>500mg TPV</th>
<th>1,250mg TPV</th>
<th>SQV/RTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>% &lt;400 copies HIV RNA</td>
<td>39%</td>
<td>55%</td>
<td>40%</td>
</tr>
<tr>
<td>% &lt;50 copies HIV RNA</td>
<td>22%</td>
<td>35%</td>
<td>30%</td>
</tr>
</tbody>
</table>

The dosing schedule and dose of ritonavir was not changed. After 48 weeks, 79% of those on the lower dose of tipranavir had viral loads below 400 copies/mL and 68% were below 50 copies. Of those on the higher dose, 50% had less 400 copies/mL and 41% had less than 50 copies. In other words, those receiving the lower dose combination had more pronounced viral load reductions—a strange outcome. Some researchers speculate this may be due to poorer adherence on the higher dose regimen. Another possible explanation is that the new formulation may not be as stable or effective as hoped. The most common side effects included diarrhea, nausea, headache, dizziness, fatigue and abnormal dreams.

Second Line Therapy with Tipranavir

A small study shows that the new protease inhibitor tipranavir is active as part of a second line regimen. This study enrolled 63 people, all of whom were experiencing a viral load rebound on their current protease inhibitor-containing regimen. Participants with an average viral load of about 32,000 copies HIV RNA and CD4+ cell counts of about 300 received two different doses of tipranavir and ritonavir (500mg tipranavir + 100mg ritonavir or 1,250mg tipranavir + 100mg ritonavir, all taken twice a day) or ritonavir + saquinavir (both dosed 400mg twice a day). In addition, all participants added two new nucleoside analogue drugs (NRTIs). Results after 16 weeks, though not statistically significant, can be seen on page 1.

Somewhat surprisingly, even though people were experiencing a viral load rebound, a large number of people did not have any protease inhibitor-related resis-

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Tolerance mutations on entry into this study. This suggests that the reason for drug failure in those cases was probably resistance to the nucleoside analogues being used, not the protease inhibitor. Not surprisingly those with no protease inhibitor–related resistance mutations had better anti-HIV responses.

The higher dose of tipranavir is not going to be pursued in future studies because of excess side effects, including nausea, diarrhea and vomiting. Instead, lower doses of tipranavir (500mg and 750mg) will be studied in combination with either 100mg or 200mg of ritonavir.

Atazanavir

Atazanavir is the newest member of the protease inhibitor class. It is expected to get FDA approval early in 2003 and is currently available in a large expanded access program. There are two main differences between atazanavir and other protease inhibitors. First, it is designed for once-daily dosing, making it easier to create a once-daily regimen that uses a protease inhibitor. Perhaps more importantly, it is the first protease inhibitor that does not appear to have a potentially harmful effect on cholesterol levels. In studies comparing atazanavir to nelfinavir (Viracept) in an otherwise common combination with d4T (stavudine, Zerit) and 3TC (lamivudine, Epivir), the group receiving atazanavir experienced no significant increase in cholesterol or triglyceride levels over 48 weeks of follow-up. Also, it appeared to at least equal the effectiveness of nelfinavir in suppressing HIV. While nelfinavir is generally considered to be among the less active PIs, it has commonly been used in comparison studies.

Another important study asked whether switching to atazanavir from another protease inhibitor would reverse the cholesterol changes caused by the other protease inhibitors. The study followed 346 people (217 men, 129 women) who had been in the earlier atazanavir vs. nelfinavir comparative study. Of the people who had previously used nelfinavir, 63 were changed to receive 400mg of atazanavir (the lower of the two doses of atazanavir used in the prior study). People who had previously been assigned to receive either 400mg of atazanavir were allowed to switch to 600mg (still once daily). All volunteers continued to receive d4T and 3TC.

Twelve weeks after the 63 people were switched from nelfinavir to atazanavir, their cholesterol levels were measured again and compared to previous levels. Changing to atazanavir obviously had the desired effect of reducing cholesterol and triglyceride levels as shown in the table above. This indicates that, at least for the first 12 weeks, switching to atazanavir has a positive effect on cholesterol. Volunteers who either stayed on 400mg atazanavir or switched to 600mg experienced no significant change in these measurements.

Changes in cholesterol levels are believed to be associated with physical changes in the body, such as fat accumulation or loss of fat in the face, arms and legs. Such changes are often called lipodystrophy.

Atazanavir Cholesterol Levels

<table>
<thead>
<tr>
<th>Lab measure</th>
<th>Comparison to pre-switch values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol levels</td>
<td>reduced 16%</td>
</tr>
<tr>
<td>LDL (bad) cholesterol levels</td>
<td>reduced 21%</td>
</tr>
<tr>
<td>Triglyceride levels</td>
<td>reduced 28%</td>
</tr>
<tr>
<td>HDL (good) cholesterol levels</td>
<td>increased 5%</td>
</tr>
<tr>
<td>% with “undesirable” total cholesterol levels</td>
<td>reduced from 32% to 10%</td>
</tr>
<tr>
<td>% with “undesirable” LDL cholesterol levels</td>
<td>reduced from 55% to 22%</td>
</tr>
</tbody>
</table>

Although some people in the original group receiving nelfinavir reported having physical symptoms of lipodystrophy, no obvious or easily measurable changes in these symptoms were noted in the people who switched to atazanavir. This indicates that 12 weeks is too short a time to see improvements, that no improvement happens or that improvements were delayed or blocked by the continued use of d4T in all study volunteers.

Unless other unforeseen side effects appear later in the study of atazanavir, the drug appears to represent an important advance in field of protease inhibitors. Only time will tell if long-term switching to atazanavir will help correct some of the fat redistribution problems experienced by people on protease inhibitors and nucleoside analogue drugs.

The expanded access program for atazanavir is quite liberal, requiring only evidence of failure on existing protease inhibitors or the presence of fat distribution problems. To apply for the program, have your doctor call 1-877-726-7327.

Bottom Line on Atazanavir

- This new protease inhibitor, designed for once-daily dosing is likely to be approved by the FDA approved in mid-2003. Thus far, it appears to be at least equal in potency to nelfinavir when used in similar combinations.
- It appears to have much less impact on cholesterol and triglyceride levels than other protease inhibitors, probably resulting in reduced risks of the fat redistribution, cholesterol-related problems (including liver problems) that have been seen with the other drugs of this class.
- It is currently available through an expanded access program to anyone who has failed on other protease inhibitors or is having cholesterol-related side effects.
New Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

CAPRAVIRINE

The future of this new NNRTI is up in the air. Lab studies suggesting long-term side effects in some animals have put future studies on temporary hold. Inflammation of the blood vessels (vasculitis) was seen in some animals receiving a high dose of the drug. This has not been observed in any of the human studies of capravirine.

Preliminary results were reported from a study of capravirine in people who were experiencing increases in viral load while on a NNRTI-based regimen. The 61 participants had an average viral load of about 10,000 copies HIV RNA and CD4+ cell count of about 300 at the start of the study. No one had previously used a protease inhibitor. All of the volunteers received nefinavir + two new nucleoside drugs and 1,400mg or 2,100mg of capravirine twice a day or placebo. There was little difference in response rates after sixteen weeks among the three groups with 60–75% of participants having viral loads below 400 copies HIV RNA. However, people receiving capravirine experienced more side effects (diarrhea), especially those receiving the higher dose. Based on this small short-term study, it is difficult to determine exactly how much, if any, capravirine is contributing to the overall anti-HIV response.

This study also shows that there is a big potential for drug interactions when combining NNRTIs as well as an increased risk for side effects. So far, there is no clear evidence of any gain in effectiveness. People should be carefully monitored if they are considering such combinations.

One of the primary concerns with the NNRTIs is the potential for rapid development of resistance, especially when used alone or part of a sub-optimal regimen. No resistance was found among any of the individuals at the end of this study.

Nevertheless, the true test for this drug will be in how effective it is for people who have developed resistance to the current NNRTIs. Only when those studies are conducted will we learn whether this drug is really different from what is currently available.

TMC-125

Early results show that a new non-nucleoside reverse transcriptase inhibitor (NNRTI), TMC-125, has potent activity against HIV. We have previously reported on a related drug, TMC-120, which also showed potent activity. Tibotec-Virco, developer of both drugs has decided to prioritize TMC-125 for further research. TMC-120 in no longer being developed. Eighteen people, all of whom had not taken anti-HIV therapy before, participated in this study. Twelve received 900mg TMC-125 twice a day for seven days and six received a placebo. After seven days of therapy, people on TMC-125 had an average viral load decrease of about 2 logs (99%) and an average CD4+ cell count increase of 100.

Larger studies with TMC-125 are planned in early 2002, including a study for people who have been on all three classes of anti-HIV drugs [protease inhibitors, NNRTIs and nucleoside analogue drugs (NRTIs)]. Other drugs in the same NNRTI class include the approved drugs nevirapine (Viramune), delavirdine (Rescriptor) and efavirenz (Sustiva). For more information about these classes of drugs, read Anti-HIV Therapy Strategies available from Project Inform toll-free at 1-800-822-7422 or www.projectinform.org.

OTHER NEW NNRTIS

There are many other NNRTIs in early development, most of which the developers claim to be at least somewhat active against viruses resistant to the currently approved NNRTIs, based on laboratory studies. These include Agouron Pharmaceuticals' AG1549, Pharmacia and Upjohn's PNU142721, MediChem Sarawak's Calanolid A and Dupont Pharmaceuticals' DPC961. Time will tell if such claims are realistic.

New Nucleoside (NRTIs) and Nucleotide (NtARTIs) Analogue Reverse Transcriptase Inhibitors

EMTRICITABINE (COVIRACIL, FTC)

Emtricitabine is a new drug considered to be similar to 3TC. The drug's development has been painfully slow but has finally reached completion. The company making FTC, Triangle Pharmaceuticals, has submitted data to the FDA seeking accelerated approval for the drug.

While there is not much excitement about FTC because it so closely resembles 3TC, regulators and advocates alike must give the drug a fair hearing. Its one clear distinction from 3TC is that it is intended to be used once a day, which is an attractive feature for many people. If FTC is otherwise just a "me too" copy of 3TC, it is unclear whether it warrants either accelerated approval or expanded access. Triangle asserts that there are other important differences between FTC and 3TC, differences that they believe warrant more interest than the drug has been given.

In the earliest studies, people receiving FTC as single agent therapy (monotherapy) for 2 weeks achieved an average 2 log reduction in viral load. Although this finding comes from a small and uncontrolled study, it is still impressive, one that rivals any protease inhibitor and appears somewhat superior to 3TC. In laboratory studies, the drug appears to be 4 to 10 times more potent, by weight, than 3TC and more importantly, seems to be slower to develop resistance than 3TC. Rapid development of resistance is 3TC's Achilles heel.

One FTC study presented at the Barcelona conference followed the experiences of 468 people receiving treatment for the first time. They received either FTC or 3TC, along with d4T and either nevirapine (Viramune) or efavirenz (Sustiva). The main study endpoint was viro-
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logic failure, defined as either failing to achieve a viral load below 400 copies, or a return of viral load above 400 copies. Both groups had similar levels of virologic failure. The main benefit seen for FTC was that fewer of the people with virologic failure while on the drug had developed resistance to FTC, compared to those on 3TC who became resistant to that drug. This suggests that more of the failures could be attributed to the other drugs in the mix and that FTC was less likely to develop resistance. It is not clear whether this difference was statistically significant, nor is it clear whether it matters much since the overall failure rate on the two treatment regimens was the same.

In two well-controlled studies comparing FTC to 3TC, study authors concluded that the drug is equivalent to 3TC in terms of anti-HIV effectiveness.

In late September of 2002, the manufacturer announced interim results from a new study comparing a once-daily combination of FTC, efavirenz (Sustiva), and ddI-EC (Videx EC) against once-daily efavirenz and ddI-EC plus twice-daily d4T (Zerit). The study, which includes 571 people (85% male), is scheduled to run for 52 weeks, but the initial analysis looked at a mix of 24- and 52-week data accumulated to date. Results are in the chart below.

The manufacturer claimed the study showed that FTC “outperformed a highly effective standard of care,” referring to the group receiving the combination of efavirenz plus ddI and d4T. While the data supports the view that FTC was part of the superior combination, the company statement was meaningless, given new information about problems with the combined use of ddI/d4T. Consequently, the ddI plus d4T combination is not considered “highly effective” and certainly not the “standard of care.” While the problems with the ddI/d4T combination may not have been clearly known at the time their study was designed, the information was available to them before they described the results of their new study. It should at least have caused them to be more cautious in promoting these new data.

The big picture seems to be that FTC is better proven in once-daily use and that it may be slower to develop resistance than 3TC, even though the failure rates of combinations using the drug are the same as when using 3TC. Larger or longer studies will be needed to determine whether FTC offers any practical advantage over 3TC. Whether all of this, taken together, warrants a special place for FTC, or expanded early access, is a decision that will have to be made by the FDA.

Gilead Sciences, maker of tenofovir, announced that it had purchased Triangle Pharmaceuticals, maker of FTC; Gilead also announced that it planned to create a new formulation of tenofovir that included FTC and tenofovir in a single pill.

**BOTTOM LINE ON EMCITRITABINE**

- This NARTI appears similar to 3TC (lamivudine, Epivir), but requires only once-daily dosing and resistance may be less likely to develop to FTC.
- More studies are needed to identify the true value and role of FTC.

**DAPD**

Early results from a small study of a new nucleoside analogue drug, DAPD, from Triangle Pharmaceuticals show promising antiviral activity. The ongoing study compared four different doses each taken twice a day: 25mg, 100mg, 200mg and 300mg.

Volunteers had not taken anti-HIV therapy before. They had an average viral load around 10,000 copies HIV RNA and CD4+ cell counts of 300–400 when they entered the study. After two weeks of DAPD alone, people taking the highest dose had the best response (about a 1.5 log or 32 times reduction in viral load). Higher doses will be studied including taking the drug once a day.

**New Targets**

**T-20 (ENFUVIRTIDE/FUZEON)**

Since enfuvirtide represents the first of an entirely new class of drugs, it is of great interest to people who have developed resistance to all or most other classes of drugs. It will, of course, work best when combined with two or more drugs that are still active, but it has shown that it can help even when people are already resistant to most other anti-HIV therapies. Enfuvirtide’s main limitation is that it cannot be made into a pill and therefore must be taken by injection twice daily. Using the drug properly is complex, as it comes in a powder that must be mixed with sterile water and then injected. The principle side effect of the drug is injection site reactions, which are seen in virtually all people taking it (though not to a degree that prevents them from using the drug). As the drug becomes more widely avail-

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**Emtricitabine Results**

<table>
<thead>
<tr>
<th>Emtricitabine Results</th>
<th>% &lt;50 copies HIV RNA (24 week data)</th>
<th>Probability of Viral Breakthrough (52 week data)</th>
<th>Mean CD4+ Increase</th>
<th>% with Treatment Limiting Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once-daily FTC + ddl-EC + EFV</td>
<td>81</td>
<td>4.7</td>
<td>152 cells</td>
<td>6.7%</td>
</tr>
<tr>
<td>Twice-daily d4T + once-daily ddl-EC + EFV</td>
<td>70</td>
<td>14.1</td>
<td>117 cells</td>
<td>13.9%</td>
</tr>
</tbody>
</table>

EFV = efavirenz  
ddl-EC = ddl enteric-coated
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The small size of the program is also something of a warning that the company might be unable to meet the initial demand for the drug when it is approved. If so, there will likely be a staged rollout of the drug, focusing first on people with the most advanced disease.

BOTTOM LINE ON T-20

- Enfuvirtide is an injectable anti-HIV drug, which is likely to be approved by the FDA in March of 2003 for people with multi-drug resistance to other anti-HIV therapies.
- It appears safe, with the primary side effect of injection site reactions.
- Enfuvirtide appears to be active and useful for people who have failed other therapies and represents a hopeful new option for people.
- Being an injectable therapy, it may be difficult to use and requires training for doctors and patients alike to administer the drug to maximize benefits and minimize side effects.

OTHER FUSION INHIBITORS

Trimeris is also studying a second generation fusion inhibitor. In laboratory studies T-1249 remains sensitive to virus that have developed resistance to T-20. Preliminary results from a small study shows that the drug does have activity against HIV; however, there were also a large number of mild-to-moderate side effects.

In the main studies submitted to the FDA, enfuvirtide was used in people who had previously developed resistance to all three classes of drugs and were in need of “salvage” treatment. At Barcelona, researchers reported on two such studies, called Toro 1 and Toro 2. All volunteers were given an “optimized” regimen composed of five to eight anti-HIV drugs and half were also given enfuvirtide. The “optimized regimen” was chosen individually for each person based on expert evaluation of resistance tests and prior anti-HIV drug history. Patient advocates applauded the study design because it closely approximated the real-world choices that people with advanced disease must face.

The main side effect reported in both studies was injection site reactions, which to some degree affected nearly 98% of the study volunteers. Not all such reactions, however, were serious. These reactions, while very unpleasant, caused only a small number people to drop out of the study. The study underlined the importance of careful training for both doctors and users in order to minimize such reactions and to maximize benefits.

While the results of Toro 1 and Toro 2 differ slightly, the basic picture is the same. In both, volunteers who received enfuvirtide on top of an optimized regimen fared much better than those receiving only the optimized regimen. In many if not most people, the drug was very likely the only fully active anti-HIV therapy in the mix. Still, the results are impressive, considering the challenge such “salvage” situations present. It is fair to say that enfuvirtide represents an important advance in the treatment of advanced HIV disease.

A major concern about enfuvirtide is likely to be cost. No drug of its type has ever been made in such large quantities before nor have even

<table>
<thead>
<tr>
<th>Toro 1: Results @ 24 weeks</th>
<th>% &lt;400 copies HIV RNA</th>
<th>% &lt;50 copies HIV RNA</th>
<th>HIV RNA change</th>
<th>CD4+ cell count change</th>
</tr>
</thead>
<tbody>
<tr>
<td>O.R. Alone</td>
<td>16</td>
<td>7</td>
<td>-0.76 logs</td>
<td>+32</td>
</tr>
<tr>
<td>O.R. + T-20</td>
<td>37</td>
<td>20</td>
<td>-1.7 logs</td>
<td>+76</td>
</tr>
</tbody>
</table>

490 people (O.R. = Optimized Regimen)
Volunteers had previously used an average of 12 different drugs.

<table>
<thead>
<tr>
<th>Toro 2: Results @ 24 weeks</th>
<th>% &lt;400 copies HIV RNA</th>
<th>% &lt;50 copies HIV RNA</th>
<th>HIV RNA change</th>
<th>CD4+ cell count change</th>
</tr>
</thead>
<tbody>
<tr>
<td>O.R. Alone</td>
<td>14</td>
<td>5</td>
<td>-0.65 logs</td>
<td>+38</td>
</tr>
<tr>
<td>O.R. + T-20</td>
<td>28</td>
<td>12</td>
<td>-1.43 logs</td>
<td>+65</td>
</tr>
</tbody>
</table>

504 people (O.R. = Optimized Regimen)
Volunteers had previously used an average of 11 different drugs.
Study will continue for 48 weeks.

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Seventy-two people with an average viral load of about 100,000 copies HIV RNA and CD4+ cell counts of 100 participated in this study. Almost all of the participants had been on previous anti-HIV therapies. Six different doses were studied ranging from 6.25mg once a day to 25mg twice a day all dosed by subcutaneous injection. Volunteers receiving the highest dose had an average 1.3 log (20 times) reduction in viral load after 14 days on the drug. Side effects included injection site reaction (mostly pain or redness in the skin), headaches and dizziness. Two serious side effects were observed, a hypersensitivity reaction to the drug and neutropenia (a reduction in neutrophils, a type of white blood cell used to fight infections).

Other fusion inhibitors in development include Progenics' PRO 542 and Lexigen Pharmaceuticals' FP-21399. Development prospects for FP-21399 have dimmed somewhat since the company ran out of money.

Cellular Inhibitor Factors

**MYCOPHENYLATE (CELLCEPT)**

Mycophenylate is an available prescription drug that may enhance the anti-HIV activity of abacavir. Most data so far come from lab studies published by David Margolis and Robert Redfield of the Institute for Human Virology (headed by Robert Gallo). The team also has started human studies.

Mycophenylate is normally used to prevent rejection of kidney transplants. Mycophenylate suppresses production of guanosine, a key building block of DNA critical to the reproduction of HIV. Researchers reasoned that the drug would be most effective if paired with an antiviral that produced "false building blocks" resembling guanosine. They realized this meant abacavir, which mimics guanosine.

This model is similar to what happens when combining hydroxyurea with ddI, though studies suggest the mycophenylate/abacavir combination may be more potent and less toxic. More importantly, lab studies show the combination is highly active when used against abacavir-resistant virus.

A key question is whether the combination adds unacceptable toxicity or immune suppression, sometimes a problem with hydroxyurea + ddI. Based on lab data, however, it appears mycophenylate can be used at doses two to ten times lower than those employed in normal application and still achieve high level anti-HIV effects.

These observations need to be confirmed in human studies, and the first have already begun. The simple two-drug combination is being given to advanced-stage patients who have failed all other therapies. Dosing employs 250mg of mycophenylate twice daily with the standard abacavir dose. The current dose of mycophenylate was chosen largely for convenience and lower doses may be tried in the future.

It is too early to recommend this for common use, but it builds upon a proven model and offers hope of a better treatment than hydroxyurea + ddI. Mycophenylate also has activity against hepatitis C virus and should also combine well with ribavirin, which is currently used in the treatment of hepatitis C. Mycophenylate should not be used with AZT or d4T as it is likely to negatively affect the activity of those drugs.

**HE-2000**

Hollis Eden recently started human studies with HE-2000. The exact way that this drug blocks HIV from reproducing has not been confirmed, although the company's current hypothesis is that it 'starves' HIV of the essential proteins that it needs. HE-2000 is given by injection directly into the muscle. In laboratory studies, this drug is also said to have activity against numerous other viruses. The drug's main claim to legitimacy rests on a small, uncontrolled study in chimpanzees, where chimps were given HE-2000 were reported to live somewhat longer than expected due to their SIV infection.

**On The Horizon**

A number of very interesting new drugs were discussed in sessions at Barcelona. Two represent new classes of therapy—entry inhibitors and integrase inhibitors—while others seek to offer improvements over drugs in existing classes. Both are welcome advances.

**ENTRY INHIBITORS**

One new class of drug is a subset of the class called entry inhibitors. The drug enfuvirtide (T-20) is one subset of entry inhibitors known as fusion inhibitors. A fusion inhibitor blocks the activity of HIV where the virus sends out a projectile, said to resemble an extremely small harpoon that anchors the virus to a CD4+ T-cell. The virus pulls itself in via this anchor until it makes direct contact with the cell. Once full contact is made, the virus inserts its genetic material into the cell.

Another subset of entry inhibitors, known as a receptor blocker (A), is conceptually similar to but distinct from, fusion inhibitors. Receptor blockers work one step before fusion inhibitors (B). Before a virus can "shoot its harpoon" and fuse with the cell, it must first find and "dock" with the appropriate cell. This step brings the virus close enough for the "harpoon" of the fusion step to be fired. It does this by producing proteins that interlock with other proteins (called receptors) on the cell's surface. The virus will ignore cells that lack the necessary receptors.
How HIV fuses to a cell

For many years, researchers knew that HIV used a receptor called CD4 to find and link up with the cell it infected, though lab data long suggested that the CD4 receptor alone did not explain all aspects of the virus/cell interaction. In mid-1996, Robert Gallo and co-workers published a key finding that showed how HIV could be suppressed by a number of naturally occurring immune chemicals known as chemokines. Within months, other researchers, most notably Edward Berger and co-workers at the National Institutes of Health, demonstrated that these chemicals affected the virus’ activity because there were receptors for them on the cells that became infected by HIV. The presence of the chemicals blocked HIV’s ability to interact with those receptors and infect the cell. The first identified of these “co-receptors” is called CCXR5. A second co-receptor, CXCR4 (also called fusin), was soon identified and associated with a form of HIV that is considered to be more destructive of T-cells and is usually seen only in advanced or rapidly progressive disease. Other co-receptors have since been identified, including CCR7, though their importance is less understood. Most of the connection activity between HIV and infected cells, however, was explained by the CD4, CCXR5 and CXCR4 receptor interactions. (For more information about HIV Co-Receptors, call the Project Inform hotline.) It stood to reason that blocking the most common receptors would help slow the activity of HIV and a race was on to find drugs that would block them. That search has now begun to bear fruit.

These drugs all work by preventing entry of the virus into the cell, but they do it by different mechanisms.

The entry inhibitor/receptor blocker farthest along in studies is SCH-C, or Schering C from Schering Plough. SCH-C works by blocking the CCXR5 receptor. The drug is currently in a phase 1 dose-ranging study that is using it as single agent therapy (monotherapy) for 10 days. The study is underway in France and the US. Although the study is uncontrolled (i.e. no one received a placebo or other drug for comparison) and results to date are from a small number of volunteers, it is clear that the drug has a significant anti-HIV effect, even at very small doses.

Testing SCH-C has been a long, slow process, largely because of a potential side effect that might affect a particular heart rhythm called the QT time. QT times were altered in some HIV-negative volunteers who used the highest dose of the drug (600mg) in the first round of studies. This effect was also observed earlier in animal studies. Because of this, the Food and Drug Administration (FDA) has required that all volunteers in these early studies have their heart rhythms continually monitored while on the drug. This requires that volunteers be hospitalized and connected to monitoring devices throughout the 10-day duration of the study. It is a fairly demanding study and has been hard to find volunteers. Those who volunteer under these circumstances are making an important contribution to the development of future drugs for HIV.

To date, the studies have shown only small changes in QT times (the side effect the FDA is concerned with) that do not seem related to the dose of the drug. Researchers, however, point out that the variations seen in QT time are small and not of the size that would be considered harmful. They also note that it is has been difficult to know whether these small changes mean anything at all, since there is no standard to compare them to. No one has measured QT times continuously for ten days to determine how much variation is normal, either in HIV-positive or negative people. It may be that small variations over time are the norm. The people who showed the most significant “events” (three or more irregular heartbeats in a row) were unaware that anything had happened, and there were no other consequences. Moreover, it is known that QT times are different in men and...
New Anti-HIV Therapies

women, further complicating analysis. Finally, it is unclear whether the effects seen in a short 10-day study are predictive of what will be seen in people who take the drug continually. For now, it is reasonable to say that no significant problems have yet been seen. The most recent round of the studies now includes a “placebo” group (people who are continuously monitored while in a hospital setting but who did not receive the drug). This may help determine what is “normal.”

Schering has a second CCXR5 inhibitor in development, currently known as SCH-D. In lab studies SCH-D appears to be more potent than SCH-C and has so far not been shown to affect QT times. Studies in HIV-positive people, however, are just beginning so it is impossible to predict whether SCH-C or SCH-D will prove more beneficial overall.

Pfizer Labs also has a promising CCXR5 inhibitor in the earliest stages of human testing but no data are yet available on this compound. A number of other companies are said to be working on entry inhibitors, but no others have yet begun human studies.

Bristol Myers has an entry inhibitor that blocks the other common receptor, CD4. Human studies of this compound have already begun, but the company has as yet provided no information, even about the design of the study. Combining a CCXR5 inhibitor with a CD4 inhibitor would seem to offer great hopes. Best-case scenario for the Schering C drug might lead to wide availability, if warranted, approximately two years from now.

One concern raised about CCXR5 entry inhibitors is whether suppressing or blocking the CCXR5 receptor might cause HIV to change to the form that uses the other receptor called CXCR4. Versions of HIV which use CXCR4, at least when they occur naturally, tend to be more aggressive and harmful than those that use CCXR5—though this is somewhat controversial. If this switch occurs, some feel it might negate the value of CCXR5 entry inhibitors and produce a worse outcome. At least one published laboratory study, however, seems to show that this does not happen. Other scientists believe that blocking the CCXR5 receptor will have no bearing on whether the virus does or doesn’t try to use the CXCR4 receptor. Time and more studies will answer this question.

INTEGRASE INHIBITORS

Another new, but long anticipated class of new drug that is finally entering human studies is the integrase inhibitors. The step in the virus’ reproduction cycle called integrase or integration occurs inside HIV infected cells just prior to the stage where protease inhibitors work. In this stage, the cell is “integrating” or bringing together the pieces of new genetic material (called DNA) made by the infected cell as it makes a copy of the virus. Many companies gave up their work on integrase inhibitors over the last several years, concluding that the goal was too difficult to make an integrase inhibitor that did not have harmful side effects. Two such drugs, however, are now in human studies. One, from Merck, is very new and is entering human use for the first time in the fall of 2002. The company has a reputation for being very demanding of new compounds before they put them through human testing, so hopes are high that the Merck compound might succeed. A second integrase inhibitor, currently being developed by GlaxoSmithKline, was originally created by the small Japanese company, Shinogi. This drug is now in phase 2 human studies. Some uncertainties exist about this drug. Although lab data have been reported on it for a number of years and this is the second year in which human testing was announced, the data released by the company only claims that the compound seems safe and that the formulation is adequately distributed in the body. It is odd though that there is no information about its anti-HIV effects. Anti-HIV data from phase 1 and phase 2 studies are never considered conclusive, but it often serves as “proof of concept” or proof that the compound is active against HIV in the body. No such information has been released about this drug, leading some to wonder whether it is working at all. It may be that the company is simply being very conservative. Only time will tell.

Commentary

While this may seem like a reasonable number of new drugs in the pipeline, their potential is limited by the fact that few if any are likely to be active against highly resistant virus, where the need is greatest. There are already many viable options for first line therapy, and reasonable, improving options for second line therapy. The new crop of drugs offers only incremental advances over these options, such as once-daily dosing. The greater challenge, finding drugs that will be highly potent despite multi-drug resistant virus, remains largely unmet, with the one proven exception of pentafuside.

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