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New Anti-HIV Therapies

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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. 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.

Tipranavir as a Second Line Therapy

	500mg TPV	1,250mg TPV	SQV/RTV
% < 400 copies HIV RNA	39%	55%	40%
% < 50 copies HIV RNA	22%	35%	30%

TPV = tipranavir; SQV = saquinavir; RTV = ritonavir

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). The 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

Table of Contents

New Protease Inhibitors
Tipranavir 1
New NNRTIs
Capravirine 2
TMC-125 2
Others 2
New NARTIs and NtARTIs
DAPD 2
New Fusion Inhibitors
Other Fusion Inhibitors 3
Cellular Inhibitor Factors
Mycophenylate 3
HE-2000 3
On the Horizon 3–5
Commentary 5

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New Anti-HIV Therapies

any protease inhibitor-related resistance 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.

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 nelfinavir + 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, though, 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 Calanolide A and Dupont Pharmaceuticals' DPC961. Time will tell if such claims are realistic.

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

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.

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New Anti-HIV Therapies

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

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 T20. Preliminary re sults 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.

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 mycophenlyate 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 effect 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 (T20) 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.

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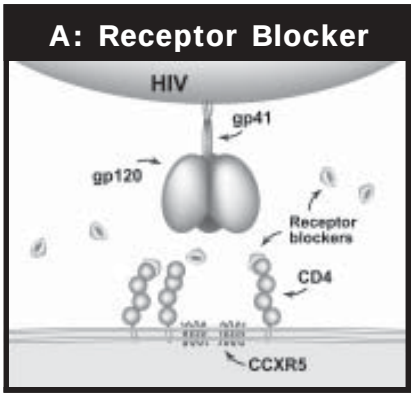
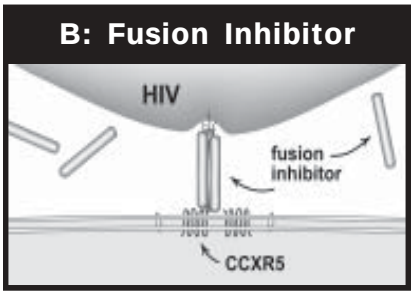
New Anti-HIV Therapies





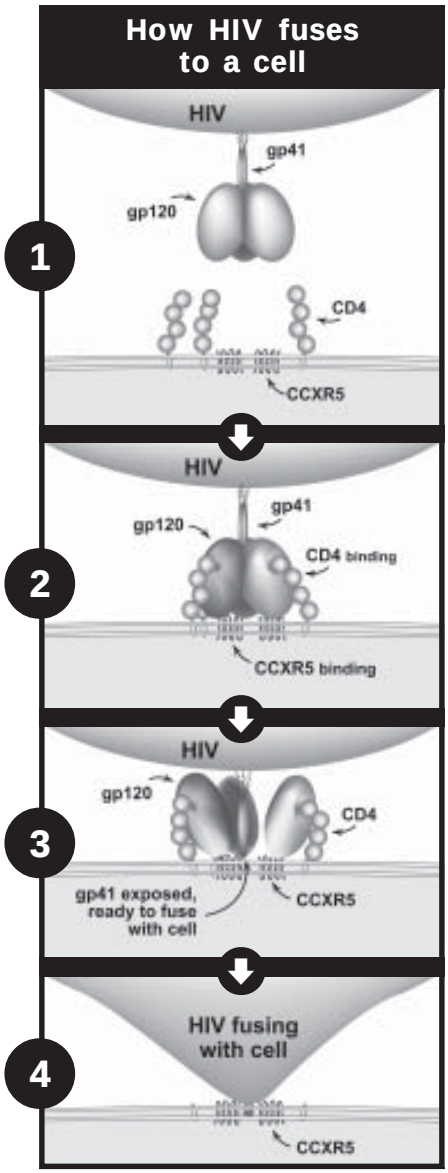
Another subset of entry inhibitors, known as a *receptor blocker (A)*, is conceptually similar to but distinct from, fusion inhibitors. Receptor blockers work one step before *fusion inhibitors (B)*. Before a virus can "shoot its harpoon" and fuse with the cell, it must first find and "dock" with the 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.

For many years, researchers knew that HIV used a receptor called CD4 to find and link up with the cells 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 volun-



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teer 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 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 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 hope. 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 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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