PROJECT inform

PERSPECTIVE

Information, Inspiration and Advocacy for People Living with HIV/AIDS

36

The Cure: We Get What We Demand

Much of the history of AIDS treatment activism can be traced back to a call for something—anything—that might change the course of HIV infection. In those early days, people typically lived only six months to a year beyond their initial diagnosis with HIV. Given such a meager outlook, people were more than happy to see the development of the first drugs that extended life for six months.

Roughly a decade later, with the arrival of protease inhibitors and three-drug combination therapy, treatment offered years of extended life. But rumblings soon followed about how difficult these therapies were to take—this one is six pills three times a day, this can't be taken with food, this must be taken with food, and these can never be taken at the same time. AIDS activists and people living with HIV then demanded simpler therapies and that's what we got—many once daily regimens in the works, drugs with fewer side effects and lower pill counts. Most regimens now are much easier to take.

After all these years, however, we remain in a place of suboptimal anti-HIV therapy options. The development and availability of these "inadequate" therapies have probably taken the pressure off the urgency and search for a cure. While therapies today are far better than those even a decade ago, *anything* short of a cure is suboptimal.

A decade ago there were three anti-HIV drugs approved. Now there are over 20, along with more sophisticated tools for monitoring one's health. More drugs are in the pipeline, including a new class called *entry inhibitors*, featured in *PI Perspective #35*. There are also entirely new anti-HIV approaches in the pipeline such as RNAi, featured on page 12. Several new drugs have recently been approved (see page 3). More tools for monitoring health and anti-HIV therapy are on the way, such as therapeutic drug monitoring (see *PI Perspective #33*). New insights into how the immune system and HIV interact have led to new directions in research. These range from ways to "flush" the reservoir of HIV-infected cells to immune restoration with human growth hormone.

Yet, as the arsenal of new drugs and strategies increases, it's easy to wonder whether each new drug promises only minor advances or if real progress is being made toward a cure. The question becomes ever more ominous as even the word *cure* now seems absent from the vocabulary of many AIDS activists, scientists and community leaders. Minor advances should not be dismissed, because until there's a cure they are certainly needed and welcomed. While these advances are merely incremental, they are advances and that *is* progress. What they are not, however, is enough.

> *While therapies today are far better than those even a decade ago,* any-thing *short of a cure is suboptimal.*

Just how close or far away is a cure for AIDS? When will there be a cure for AIDS? The simplest answer is that we're as close as we are far away. The cure might be being identified this very moment, in a laboratory somewhere, and it's possible that the scientist doesn't even wholly know what she or he is looking at. It's possible that realizing a cure for AIDS will be a laborious process, taking years to identify, research and refine. It's likely that a real cure won't be a simple pill or medicine, but rather a complex process that ultimately rids the body of HIV or renders this virus harmless. Regardless of the case, there are a few things that are likely true. One is that we get what we demand. The other is that we simply do not have enough information to be pessimistic.

The demand for a cure needs to be put back into the community's lexicon. We must reclaim it and hold our leaders, activists, doctors, researchers and the bureaucracies that govern research priorities accountable for making it the goal. History shows that people living with HIV hold an incredible amount of power, even when the odds are stacked against them. People living with HIV and their advocates have changed the system that evaluates and approves new drugs, created mechanisms for earlier access to experimental therapies and continue to influence the conduct of research at nearly

October 2003

In This Issue

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every level. These changes are revolutionary, but they are also not enough. They are a start and they're a great start. We have further to go.

There are more activist issues to work on than ever before. The current administration hasn't been friendly to AIDS, either for research or for programs that serve people living with HIV/AIDS. More voices are are needed in the fight for the full spectrum of programs that serve people's needs. The use of newer anti-HIV drugs has left a wake of unanswered questions about side effects and strategies on how best to use them. (The next issue of *PI Perspective* will be dedicated to examining strategies.) How drugs interact, how they work in different populations (see page 15), and how drug pricing is impacting healthcare costs and services are all much more complicated today than just ten years ago. The number of activists, however, has not grown proportionally with the number of issues.

There are challenges for all involved in the pursuit of a cure that we must acknowledge, address and overcome. As time has passed, many have grown weary. For those living with HIV, the draining effects of struggling to manage their health, grief and loss cannot be overstated. For the tenacious activists pushing the boundaries of science toward a cure, the years are scattered with failures. For some activists, even the word *cure* evokes a sense of failure or embarrassment that there was ever hope for a cure.

Hundreds of threads of discovery are left dangling, however. One of those threads may well be the path to the cure.

Similarly, many researchers have settled into their careers, wrapping themselves in the minutia of studies that lack creativity and inspiration and lead nowhere. Pessimistic scientists stuck in the belief that people can never get rid of a virus need to be reminded of the folly of the word *never*. It's staggering to reflect upon how many *nevers* have been achieved through inspired scientific pursuit. Many skeptical scientists contended that humans would never fly or walk on the moon and the idea of a heart transplant was pure blasphemy. These *nevers* are now simply part of the legacy of scientific progress.

As the pandemic now spans generations, newly infected young people don't have the knowledge or experience of a world without AIDS as a touchstone. They do not know what has been taken from them. Many are crippled by a belief that they should have known better or that somehow they deserve HIV infection. The newly infected must find their courage and their voice and they have every right to stand shoulder-to-shoulder in the fight to live in a world without AIDS. And this includes the courage to demand and participate in the groundbreaking research that will lead to a cure for AIDS.

It's time to reinvigorate the search for the cure among ourselves, and inspire others who have not known a world without AIDS to realize that a cure is possible. In the 1980s and 1990s, a large part of the AIDS activist movement was formed and galvanized around the notion of being united in anger to end the AIDS crisis—ordinary people angry that partners, friends and children were shunned, denied care and dignity. Great things were accomplished as a result of this motivated, focused anger. Today, there is still one huge reason to be angry: more people than ever before are living with HIV/AIDS. In many places, people are still dying shunned, alone and without medical care or medication. Anger can still be a motivator to action, but it likely cannot sustain a movement for the long-haul. *What do you have to live for?* The diverse answers to this question are the foundation of a sustainable movement. As we take inventory of what we have to live for and use it as the basis to inspire and motivate us, we can create a movement with room for compassion, grieving, healing, anger and visions of our lives, our futures and our communities in a world without AIDS.

Scientific breakthroughs in understanding HIV occur on a near daily basis. Understanding, however, must be turned

© PI Perspective is published three times per year and is distributed free of charge. PI Perspective is a publication of:

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into action and focused on curing AIDS, not just knowing everything imaginable about it. The biological mechanisms of the polio virus, for example, were not understood until decades after the disease was all but eliminated. The community is needed in the scientific process to press the urgency of bringing sometimes disparate discoveries together and turning ideas into areas of therapeutic exploration. This is happening right now with pushing the research of new classes of drugs, like *entry inhibitors*. Hundreds of threads of discovery are left dangling, however. One of those threads may well be the path to the cure.

For those who give up hope for a cure and for those who don't believe it will come in their lifetime, there are simply no data or objective facts that support those beliefs. What is true is that the possibility of a cure for AIDS exists today and it's our challenge to help find it. This does not mean that everything under the sun needs to be researched, but rather a strategic plan to research and eliminate viable possibilities needs to be devised and pursued.

For some, current therapies may actually be *enough* to lead to full life spans. Most people's therapy fails over time, however. People continue to die of AIDS, and more find themselves in a place where the drug arsenal simply isn't good enough or can't be tolerated indefinitely. No matter how well therapies work for some they can dominate a person's life, leaving one less secure to count on themselves and pursue visions of their lives and their own futures. The goal must be a cure

As we take inventory of what we have to live for and use it as the basis to inspire and motivate us, we can create a movement with room for compassion, grieving, healing, anger and visions of our lives, our futures and our communities in a world without AIDS.

There is no reason to believe the future holds anything other than continued progress. History also shows us involving people with HIV/AIDS in the process speeds its progress. If what we demand is a cure for AIDS, then there's no reason to believe we won't get there.

Project Inform has taken up this challenge. This year we've renewed our commitment not to focus our attention on "*me too*" drugs, new versions of the same therapies that promise only incremental advances. We will increase our focus on research reform to remove barriers to testing innovative therapy approaches and reinvigorate efforts on projects that will advance science toward a cure.

We will also raise the issue of a cure at every scientific conference and venue where we have a presence. We invite you to come along with us in the fight for a cure, and we support you in finding your own path. If you would like a list of things you can do to help in the fight for a cure, email *TAN@projectinform.org*.

Our history shows us that a few people *can* make a vast difference. More people can make an even greater difference. So how do we ensure that a cure be realized today as opposed to tomorrow—this year rather than next? The first step is believing that we *can* make a difference, or at least suspending a belief that we cannot, and finding our voice and simply trying. There is no harm in trying—there is merely the possibility of success or the possibility of failure. But it leaves us no worse off than yesterday. Change will never happen without first finding the will and courage to make it happen. ■

New Anti-HIV Drugs Receive FDA Approval

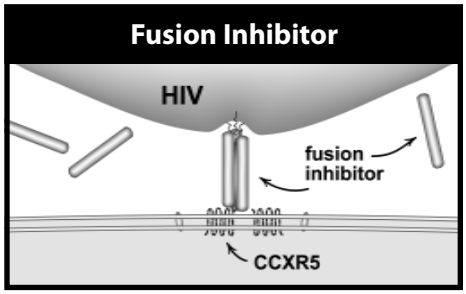
Three anti-HIV drugs have recently been approved by the Food and Drug Administration, including one in a new class called *fusion* or *entry* inhibitor. Each adds something unique to the arsenal of therapies to treat HIV infection. The three include:

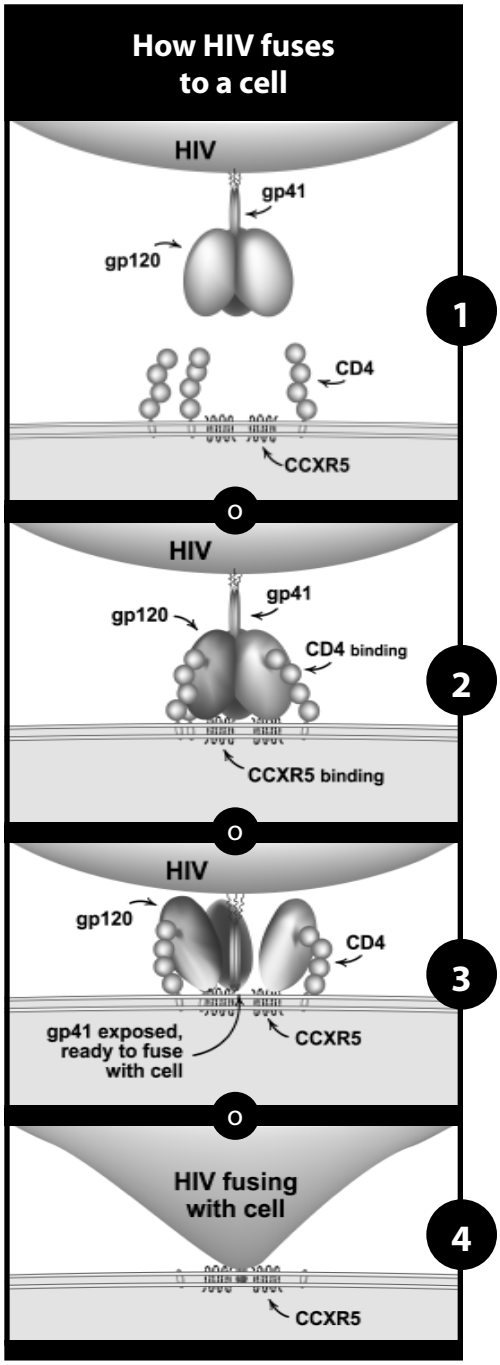
Drug Name	Trade Name	Company	Drug Class
T-20, enfuvirtide	Fuzeon	Hoffman La-Roche, Trimeris	entry inhibitor
FTC, emtricitabine	Emtriva	Gilead	nucleoside analog reverse transcriptase inhibitor
Atazanavir	Reyataz	Bristol Meyers Squibb	protease inhibitor

The following articles on pages 4–10 highlight information on each of the newly approved drugs and provide a discussion on how they fit into the arsenal of existing drugs.

Enfuvirtide (Fuzeon)

The FDA approved enfuvirtide (Fuzeon) in spring 2003 to use with other anti-HIV drugs in children age six and older and in adults who have used anti-HIV therapy before. Enfuvirtide is in a new class of drugs called *entry inhibitors*. The drug works at the start of HIV's reproduction cycle by blocking its ability to infect an immune cell. This occurs at the point when HIV fuses to the cell's outer wall in order to gain entry into it (see graphics to the right). For more information, read *New Hope for New Classes of Therapy* in *PI Perspective 35*.





Who should use it?

Studies to date include people who have used and may have resistance to many drugs, and who have few options to put together a potent combination of drugs. For these people, enfuvirtide was able to reduce HIV levels and provide benefits. While enfuvirtide shows some activity in people resistant to many or all anti-HIV drugs, studies suggest it may be most effective in reducing HIV levels when used with at least one or two drugs that are still active against HIV. Because of its cost and the difficulties associated with using it, enfuvirtide is not recommended for first-time therapy or after only a few other drugs have been tried.

What does the research show?

Results from two major studies (TORO 1 and TORO 2) were pivotal in the FDA's approval. Both included people with extensive use of anti-HIV therapy who were unable to control viral load. In each study, at study entry, CD4+ cell counts averaged below 100 and HIV levels averaged 100,000. TORO 1 included 491 people and TORO 2 had 504. In both, people used three to five anti-HIV drugs with or without enfuvirtide.

More people who used enfuvirtide reached undetectable viral loads and higher CD4+ cell counts. Of those on enfu-virtide, 37% (TORO 1) and 28% (TORO 2) achieved viral suppression below the limit of detection of the test compared to 16% (TORO 1) and 14% (TORO 2) of those not using it. Average CD4+ cell count increases among those on enfuvir-tide were 76 (TORO 1) and 65 (TORO 2) compared to 32 (TORO 1) and 38 (TORO 2) in the group not taking the drug.

Another way to check the success of a regimen is its ability to decrease viral load by 1 log, regardless of whether or not a person reached "undetectable" levels. When combining results from both studies, slightly more than half of those on enfuvirtide had at least a 1 log reduction compared to about 25% of those not using the drug.

How to use it?

Enfuvirtide cannot be made into pill form for oral use and must be taken by injection. It is injected beneath the skin (not in a vein or muscle), twice a day about 12 hours apart. Each dose is 90mg, for a total daily dose of 180mg. For children weighing less than 94 pounds, doses are based on body weight (2mg/kg twice daily).

The drug is a powder and needs to be mixed with sterile saline solution. A prescription includes these, along with syringes and a sharps container for disposing of used syringes. Your doctor should give you information on how to mix the drug and provide guidance on self administration. Preparing the mixture and the injection site takes about 45 minutes, including the time it takes for the powder to dissolve. Unfortunately, the drug cannot be prepared ahead of time for several days use and should not be stored in the syringe to use later. Because injection site reactions may occur it's important to change the injection site. Re-using syringes may lead to serious infections and should be

avoided completely.

What about side effects?

The most common side effect, which occurred in almost everyone, is some degree of injection site reactions (redness, itching, swelling or skin irritation where the drug was injected into the skin). While this can be troublesome, only 5% of people stopped using the drug because of these side effects. In about 9% of people, however, reactions were severe enough to limit their activity and/or need an intervention to manage the reactions. Follow the training you receive from your doctor on how to use the drug; it is critical to minimizing these injection site problems. If you are not given guidance on how to do this, speak to your doctor and insist upon it. Other possible side effects, occurring in a small percentage of people taking the drug, include feeling tired (*fatigue*), sleep disturbance (*insomnia*) and pain or tingling in the legs, arms, hands and/or feet (*peripheral neuropathy*).

A small percent of people have a hypersensitivity (like an allergic) reaction to enfuvirtide, which could be life-threatening. Symptoms may include fever, chills, nausea, vomiting and shivering (*rigors*). People having these symptoms should contact their doctors immediately. Stopping the drug permanently may be necessary. For reasons that remain unclear, a slightly higher rate of bacterial pneumonia occurred among those using enfuvirtide.

What about drug resistance?

As with other anti-HIV drugs, HIV can develop resistance to enfuvirtide. Resistance occurs when the virus changes or mutates and the drug no longer controls the reproduction of HIV. However, studies suggest that enfuvirtide is effective against virus that has developed resistance to all other approved anti-HIV drugs.

Cross-resistance occurs when resistance to one drug makes other drugs less effective. If, or as other drugs like enfuvirtide become available, cross-resistance to similar drugs is possible. However, a similar drug that the company is working on (called T-1249) has shown activity against virus that's resistant to enfuvirtide. T-1249 will also be an injection, but hopefully will require less frequent injections.

Are there concerns about drug interactions?

Studies have been done with other anti-HIV drugs and rifampin, a common tuberculosis medicine. Drug interactions were minor and did not require adjusting the dose of any drug. Whether or not enfuvir-tide interacts with other drugs, like methadone, psychiatric medicines or street drugs, is not known. People are encouraged to discuss the possible drug interactions between ***all*** of the therapies and substances they are taking with their doctor and/or pharmacist.

Discussion

Perhaps the most important thing to think about when considering a new drug is how it fits into the arsenal of current therapies. Enfuvirtide will likely never be considered as part of a *first line* regimen—for someone who has never used anti-HIV drugs. This is because it's difficult to prepare and inject, and injection site reactions can be problematic. This drug may not even be very appropriate as part of a *second line* regimen—for someone who has used one regimen and is looking for other options due to drug failure or side effects. Ultimately, the optimal role of this drug is as part of a *third line* or *salvage* therapy regimen.

Third line or *salvage* therapy often refers to a regimen for someone who has extensively used anti-HIV drugs and has developed resistance to many drugs in most classes. However, a *true* salvage therapy situation is when prominent resistance occurs to all drugs in all classes. It's fairly rare for people to be in true salvage situations. Often, when looking at resistance test results and evaluating the history of anti-HIV drug use, many if not most people, while working with their doctors, can put together regimens that are active against HIV.

But ***how*** enfuvirtide fits into the picture of *third line* therapy is not wholly clear. If people can construct regimens—with the guidance of a doctor and resistance test results—that they believe will be potent without adding enfuvirtide, it may be a great option to hold enfuvirtide until later if or when options narrow even further. With that said, however, data show that enfuvirtide works best when paired with at least one other drug (preferably two) that's active against HIV. Thus using enfuvirtide in a *true* salvage situation, when resistance to all drugs is likely, is not the best use of the drug.

For people facing *third line* therapy choices, enfuvirtide might not be the first option to turn to if other ones are available. A new protease inhibitor called tipranavir looms on the horizon. This drug will likely be available through expanded access programs in late 2003 or so. It appears to be active even in the face of resistance to all other protease inhibitors.

For some making *third line* therapy decisions, holding off on using enfuvirtide until tipranavir becomes available may still allow for using a viably potent regimen made up of drugs with only partial resistance. For others, in *true* salvage situations, holding off on using enfuvirtide until tipranavir is available may provide two new and potent drugs to pair up for hopefully better results. Finally, while enfuvirtide appears more potently able to impact HIV when paired with other anti-HIV drugs that are active against a person's virus, it still provides some benefits in *true* salvage situations, even if it can't be paired with another completely new drug. The results, however, may be short-lived in such situations. For more complete information on enfuvirtide, call Project Inform's toll-free National HIV Treatment Information Hotline at 1-800-822-7422. ■

Project Inform Online

If you are looking for HIV/AIDS treatment information, log onto Project Inform's HIV/AIDS treatment website at:

www.projectinform.org

FTC (emtricitabine, Emtriva)

The FDA approved FTC (emtricitabine, Emtriva) in July 2003 for use by adults in combination with other anti-HIV drugs. FTC is a *nucleoside analog reverse transcriptase inhibitor* (NRTI). Other drugs in this class include 3TC, abacavir, AZT, Combivir, d4T, d4T XR, ddC, ddI, ddI EC and Trizivir.

Who should use it?

FTC is very similar to 3TC. Thus far it has shown relatively few side effects. The advantage of FTC's once daily dosing may appeal to those trying to simplify their regimens.

What does the research show?

Several studies support the approval of FTC. One included 571 people who had never taken anti-HIV drugs. Volunteers received ddI and efavirenz with either FTC or d4T. After 48 weeks (nearly one year), 81% of those receiving FTC sustained undetectable viral loads compared to 68% on d4T. CD4+ cell counts increased about the same between the groups, though slightly higher for FTC recipients. More people on d4T quit the study because of side effects—22% on d4T vs. 15% on FTC.

In another study, 440 people used either FTC (once daily) or 3TC (twice daily) with other anti-HIV drugs. Before study entry, all were on effective, standard therapy including 3TC along with other anti-HIV drugs for at least 12 weeks. People stayed on their regimens but were randomly assigned to either continue on 3TC or switch to FTC. After 48 weeks, outcomes were similar. Side effects were fairly similar between the groups.

In general, results from these two large studies suggest that FTC may be slightly more active and have fewer side effects than d4T. FTC appears to have similar activity and with comparable side effects to 3TC.

How to use it?

FTC is a 200mg pill, taken once daily, with or without food. FTC's once daily dosing makes it attractive to use. Dose changes are likely needed for people with kidney complications, including those on dialysis.

What about side effects?

FTC has relatively few side effects. The most common ones include headache, diarrhea, nausea and rash. Only 1% of volunteers quit the studies due to these side effects. Generally speaking, the levels of side effects were similar with FTC as with other regimens, such as those using d4T or 3TC. A noted exception was skin discoloration of the palms of hands and/or soles of feet among those on FTC. There were no other symptoms related to this discoloration, and researchers aren't sure what is causing this side effect.

In addition to being active against HIV, FTC appears to be active against hepatitis B virus (HBV). People with both HIV and HBV have faced a worsening of HBV-related complications after stopping FTC. For this reason, it's recommended that people living with both use caution when taking FTC, as it has not been tested well in this setting. Moreover, careful monitoring of HBV should follow after stopping FTC.

A relatively rare but serious side effect from using NRTIs is severe chemical imbalances in the body called *lactic acidosis*. For more information on lactic acidosis, read Project Inform's publication, *Mitochondrial Toxicity*, as well as new information on ddI and d4T in *PI Perspective 35*. Also, the use of anti-HIV drugs have been linked to changes in body shape and fat distribution. NRTIs may be particularly associated with loss of fat, such as facial or limb wasting. For more information, read Project Inform's publication, *Lipodystrophy*.

What about resistance?

Resistance to a drug occurs when the virus changes or modifies itself such that it is no longer crippled in its replication cycle by the effects of a drug. Resistance to FTC may be slow to develop when used with other anti-HIV drugs. However, HIV resistance to FTC has been seen.

Cross-resistance is when resistance to one drug also causes resistance to other drugs. Studies suggest that once HIV has developed resistance to FTC, then 3TC and ddC may be less effective. FTC and 3TC share similar resistance patterns, so virus resistant to 3TC will likely be resistant to FTC as well. Test tube studies suggest that HIV showing certain types of resistance to abacavir, ddI, tenofovir or ddC may also be less susceptible to FTC.

Are there concerns about drug interactions?

It's not expected that FTC will have many drug interactions. Studies have been conducted with a few other anti-HIV drugs and no interactions were observed. Whether or not FTC interacts with other medications (methadone, psychiatric medicines, street drugs, etc.) is not known. There are possible interactions with other drugs that are cleared through the kidneys. People are encouraged to discuss these interactions between ALL of the therapies and substances they are taking with their doctor and/or pharmacist.

Discussion

Some consider FTC to be a "me too" NRTI: just another drug in a growing list with no special benefits. Data suggesting that FTC is superior to d4T may have been important a year or so ago when d4T was among the most used and seemingly favored NRTI among patients and providers. However, the use of d4T has waned because of its implicated role in fat loss and liver complications.

How FTC compares to 3TC is perhaps more important. 3TC has long been regarded as one of the most potent NRTIs when used correctly with other potent drugs. The arrival of Combivir as a single pill, taken twice daily, made three-drug therapy immensely easier. Combivir provided two NRTIs as the backbone for a potent three-drug regimen. Doctors and patients alike sighed in relief at the new formulation that helped ease the pill burden and improve adherence

Ultimately the question is what does FTC add to the anti-HIV arsenal? It appears to be a fairly potent NRTI and similar in many ways to 3TC. Like 3TC, it has relatively few side effects (though slightly more than 3TC). One nice advantage is that FTC is taken just once daily. This benefit may be less critical now that more and more drugs are coming out in once daily formulations, however.

Gilead Sciences, who developed FTC, also makes another anti-HIV drug called tenofovir. It is also taken once daily. It is Gilead's goal to make them into a single pill taken once daily, allowing for a potent combination in one pill. With the new protease inhibitor atazanavir (also dosed once daily) and other advances on the horizon, it may soon be possible to construct potent three-drug regimens that need as few as one or two pills once daily.

FTC thus represents a sort of dawning of a new and important phase of refinement in HIV treatment—that is, drugs that are easier to take with fewer side effects and good potency. In and of itself, it offers very little in the short-term. Its real benefits likely won't be realized until it's co-formulated with tenofovir. The company hopes to launch this new pill in 2005. ■

Atazanavir (Reyataz)

Atazanavir (Reyataz) is a protease inhibitor that received FDA approval in June 2003. Other approved drugs in this class include amprenavir, indinavir, Kaletra (ritonavir+lopinavir), nelfinavir, ritonavir and saquinavir.

Who should use it?

Atazanavir is a once-daily therapy approved for use in combination with other anti-HIV drugs in adults, regardless of prior anti-HIV therapy use. It's recommended that people receive a resistance test prior to starting the drug to increase the chance that they will benefit from it. The drug does not appear to cause large increases in cholesterol and triglyceride (lipid) levels associated with other protease inhibitors. For this reason it may be a nice option for people with cholesterol concerns and/or those with risks for heart disease.

When used as part of a second or third line therapy, in order for atazanavir to provide benefit, it may well need to be "boosted" with a small amount of ritonavir. Because ritonavir is known to have an effect on cholesterol, the advantages of atazanavir with regard to this side effect may be decreased.

What does the research show?

Three studies were particularly important in supporting the approval of atazanavir. One compared atazanavir to a commonly used NNRTI drug called efavirenz. Another compared atazanavir to the protease inhibitor nelfinavir. Both of these studies included people who had never used anti-HIV drugs. The third study compared atazanavir to the protease inhibitor Kaletra and included people who had previously used (and failed) one protease inhibitor-containing regimen. In all studies, CD4+ cell counts at study entry were about 300 (321 in the first, 295 in the second and 318 in the third). In the studies that looked at people who had never used anti-HIV treatment, viral loads were about 60,000 at study entry. In the study of people who had used and failed one protease inhibitor, viral load was close to 10,000 at study entry.

In the first study, 810 volunteers received Combivir (AZT+3TC, given twice daily) and either atazanavir (400mg once daily) or efavirenz (600mg once daily.) Both groups had comparable decreases in viral load and rises in CD4+ cell counts. Overall, about 65% of those receiving the combinations achieved viral load suppression to below the limit of detection of the tests (400) through 48 weeks (about one year) of therapy. Those

Atazanavir vs. efavirenz; 810 people after 48 weeks

Regimen	% with viral load under 400	CD4+ cell count increase
Combivir + ATV	65%	180
Combivir + EFV	65%	160

ATV = atazanavir; EFV = efavirenz

Atazanavir vs. nelfinavir, 467 people after 48 weeks

Regimen	% with viral load under 400	CD4+ cell count increase
Atazanavir + d4T + 3TC	67%	234
Nelfinavir + d4T + 3TC	59%	211

receiving ata-zanavir had a mean (average) CD4+ cell increase of close to 180, while those taking efavirenz averaged increases of about 160. In general these therapies appear to be comparable in potency, though have different side effect concerns.

In the second study, 467 people were given d4T and 3TC twice daily in combination with either atazanavir (once daily) or nelfinavir (1,250mg twice daily). Similar percentages of people achieved viral suppression to below detectable (400) in both groups, but those taking atazanavir did slightly better (67% compared to 59%) though 48 weeks. However, when using a more sensitive viral load test (limit of detection less than 50) slightly more people did "better" in the nelfinavir group (38% compared to 33%). CD4+ cell count increases averaged about 234 among those receiving atazanavir compared to 211 nelfinavir recipients. In other words, these therapies appear generally comparable in potency, though again they have differing side effect concerns.

The third study evaluated once daily atazanavir to twice daily Kaletra in combination with two NRTI drugs (like AZT, 3TC, d4T, etc.). Significantly more people receiving the Kaletra-based regimen achieved viral load reductions to below the limit of detection (75% compared to only 54% of those taking atazanavir) through week 24 (6 months). When using the more sensitive viral load test, with a limit of detection of 50, these results held with 50% of Kaletra users and only 34% of atazanavir users achieving suppression to undetectable levels. Moreover, CD4+ cell count increases were more pronounced among Kaletra recipients (121 compared to 101 receiving atazanavir). While Kaletra was clearly a superior option, those receiving Kaletra also experienced more side effects.

In a recent study presented at the International AIDS Society meeting (July 2003), atazanavir was evaluated as part of a third line regimen in 358 people who had failed two previous anti-HIV regimens and demonstrated resistance to at least one drug in each class (NRTI, NNRTI and PI). Volunteers received tenofovir and an NRTI drug and either Kaletra, once daily combination of atazanavir (300mg) + ritonavir (100mg) or once daily combination of atazanavir (400mg) + saquinavir (1,200mg). At 24 weeks (6 months) the Kaletra and atazanvir+ritonavir groups showed comparable results, with the atazanvir+saquin-avir combination falling out as inferior. Those receiving the atazanavir + ritonavir combination were less likely to have increases in lipid levels, less likely to experience diarrhea, but more likely to have increases in bilirubin and associated jaundice. Because atazanavir may boost tenofovir levels, however, it's unclear if these same results would hold true if the atazanvir+ritonavir combination were used in conjunction with any NRTI two-drug backbone for a regimen.

For results of an earlier study comparing atazanavir to nelfinavir, and switching from nelfinavir to atazanavir, see *PI Perspective # 35*.

How to use it?

Atazanavir comes in 100, 150 and 200mg capsules. The daily dose for adults is 400mg, once daily, to be taken with food.

Dose adjustments are required when using the drug in combination with some other anti-HIV drugs including efavirenz, ritonavir and tenofovir. With other drugs there are guidelines for use when they are used at the same time (e.g., ddI and ddI EC in combination with atazanavir). For more information about dosing adjustments and concerns, call Project Inform's hotline.

Other dose adjustments may be required when taking atazanavir in combination with other anti-HIV drugs as well and if people have impaired liver function.

In general, boosting with a small dose of ritonavir is recommended for most people who have developed resistance to other protease inhibitors.

What about side effects?

Perhaps the most attractive feature of this drug, besides the ease of use of once-daily dosing, is that, so far, studies have shown relatively few side effects. This may or may not change as doctors and patients have more and longer-term experience with the drug. One of the most common side effects of atazanavir is increases in a laboratory

Three New Drugs: Buying and Access

Atazanavir, emtricitabine and enfuvirtide are available by prescription. Some states may cover these drugs through their AIDS Drug Assistance Programs (ADAP). For information on your state ADAP eligibility and to find out if these drugs are covered, contact Project Inform's toll-free Hotline at 1-800-822-7422. Information is also available through the AIDS Treatment Data Network at 1-800-734-7104 or *www.atdn.org*. People who lack insurance, Medicaid, ADAP coverage or cannot afford to pay for the drug can sometimes gain free access to them through the manufacturer's Patient Assistance Program.

Atazanavir: 1-800-272-4878

Emtricabine: 1-800-445-3235

Enfuvirtide: 1-866-694-6670

Currently, supplies of enfuvirtide are limited, so the company has set up the "Progressive Distribution Program." Doctors apply on behalf of their patients. Once the supply meets the ongoing needs of the individual, the prescription is "activated" and the drug is shipped either to the patient or doctor. Prescriptions are filled on a first-come, first-serve basis. For more information, doctors should call 1-866-694-6670 to enroll their patients. Thereafter, patients may call directly to check on their status and ask questions. Enrollment forms are available at *www.fuzeon.com*.

measure called bilirubin. This occurred in 35% and 47% of study participants in the first two studies noted above. In nearly all cases bilirubin levels returned to normal upon discontinuing the drug. In a few instances physical symptoms were associated with this elevated lab marker, including yellowing of the skin or whites of the eyes (jaundice).

Atazanavir does not appear to have the pronounced impact on lipid levels (cholesterol and triglycerides) seen with most other protease inhibitor therapies. When compared to Kaletra, atazanavir appeared to cause dramatically fewer problems with lipids. Some speculate that this might lead to decreases in concerns about body composition changes (particularly fat accumulation in the truncal area, breast or base of the neck) called lipodystrophy associated with protease inhibitor use. Preliminary reports from a study which looked for body composition changes in people receiving either an efavirenz- or atazanavir-containing regimen with AZT+3TC showed no symptoms of lipodystrophy through 48 weeks of treatment. While some people receiving efavirenz had increases in lipids, no one receiving atazanavir had increases in lipids. It can't be said that atazanavir use won't be associated with lipodystrophy, certainly longer follow and more study is needed, but this preliminary report is encouraging.

When compared to nelfinavir or efavirenz regimens, atazanavir-contain-ing regimens appeared to have similar or slightly fewer side effects. In general, when compared to efavirenz, slightly more people receiving atazanavir experienced nausea (feeling sick) and yellowing of hands/eyes (jaundice). Some of the biggest concerns with efavirenz include sleep disturbances, mental status changes, including depression. These did not occur as often among those receiving atazanavir. With regard to nelfinavir, where the most common side effect is diarrhea, significantly fewer people experienced diarrhea with atazanavir. Also, when people who had used nelfinavir in the first part of a study were later switched to atazanavir, there were significant drops in their cholesterol levels.

Protease inhibitors have been associated with an increased risk of diabetes. In the study which compared atazanavir to efavirenz in combination with AZT+3TC, noted above, at 48 weeks no one in either group showed evidence of insulin resistance, which is a measure for risk of diabetes. Diabetes may also be less of a concern with atazanavir compared to other protease inhibitor drugs.

As with other protease inhibitors, it's possible that symptoms of hepatitis C or B may worsen upon starting atazanavir. People are encouraged to be tested for hepatitis prior to starting anti-HIV drugs and monitor liver tests carefully after starting anti-HIV therapy.

What about resistance?

HIV resistance to atazanavir is likely to be a concern, and thus the drug should be used in combination with other anti-HIV therapies. Resistance to a drug occurs when the virus changes or modifies itself such that it is no longer crippled in its replication cycle by the effects of a drug. Cross-resistance is when resistance to one drug also causes resistance to other drugs. Studies suggest that cross-resistance to other protease inhibitor drugs, in particular, is likely to be a problem with atazanavir.

Once a person has developed resistance to atazanavir, they are very likely not going to benefit as well from other approved protease inhibitors. It might be possible, however, to use boosted doses of these other therapies to overcome some of this resistance. Some test tube studies suggest that even though resistance may have developed to some other protease inhibitors, atazanavir may still have some anti-HIV effect. The bottom line message, however, is that the story of atazanavir resistance is still an evolving story.

Are there concerns about drug interactions?

Atazanavir is processed through the liver and has many drug interactions. Some of these interactions may be life-threatening, others may merely require dose adjustments of the therapies. For a list of known and suspected drug interactions, call Project Inform's hotline and request the publication, *Atazanavir*.

Drug ID Chart

GENERIC NAME	TRADE NAME
Protease inhibitors	
amprenavir	Agenerase
atazanavir	Reyataz
fosamprenavir	Lexiva
indinavir	Crixivan
lopinavir + ritonavir	Kaletra
nelfinavir	Viracept
ritonavir	Norvir
saquinavir hard gel	Invirase
saquinavir soft gel	Fortovase
NRTI (nucleoside) and NtRTI (nucleotide) analogue reverse transcriptase inhibitor	
abacavir	Ziagen
didanosine (ddI)	Videx
didanosine enteric-coated (ddI EC)	Videx EC
emtricitabine (FTC)	Emtriva
emtricitabine + tenofovir	Truvada
lamivudine (3TC)	Epivir
stavudine (d4T)	Zerit
stavudine extended release (d4T XR)	Zerit XR
tenofovir	Viread
zalcitabine (ddC)	Hivid
zidovudine (AZT)	Retrovir
3TC + AZT	Combivir
3TC + AZT + abacavir	Trizivir
3TC + abacavir	Epzicom
NNRTI (non-nucleoside reverse transcriptase inhibitor)	
delavirdine	Rescriptor
efavirenz	Sustiva
nevirapine	Viramune
Fusion inhibitor	
enfuvirtide (T20)	Fuzeon

Discussion

It remains a bit unclear how atazanavir fits into the arsenal of other approved protease inhibitor drugs. The most attractive features of this drug are its ease of use (it only needs to be taken once daily), and its relatively few side effects. These features may make it of particular interest as part of first line therapy for treating HIV, for those who are experiencing problems with adhering to more complex medication schedules, for those who are experiencing problems with lipid elevations (increases in cholesterol and triglycerides) while using other therapies and for people who may have risks for high cholesterol and heart disease (e.g., family history, smokers, etc.).

When considering atazanavir as part of a regimen if you've never used anti-HIV therapies before, there are a few issues to consider. First, in studies atazanavir appeared to have equal potency when compared to efavirenz-containing regimens. Efavirenz is in a different class of drug, it's an NNRTI, and it is a very popular drug for first line use. The advantages of starting with atazanavir as opposed to efavir-enz may be that atazanavir does not have the mental status side effects associated with efavirenz (like sleep disturbances, hallucinations, etc.). Also, when someone develops resistance to efavirenz, nearly complete cross-resistance to all the other currently available NNRTIs is very likely (i.e., the other NNRTIs are likely to not work at all). While there is some evidence that resistance to atazanavir may also lead to cross-resistance to other protease inhibitors, it's less clear if this will present a major obstacle in benefiting from other protease inhibitor-containing regimens in the future. Also, because atazanavir need only be taken once daily, especially for someone starting therapy for the first time this may be very attractive as it may decrease the interference with daily routines while a person adjusts to taking anti-HIV medications.

When it comes to atazanavir use as part of second line therapy, the picture becomes a little more complicated. Resistance testing will be particularly important here to help determine if a person is likely to benefit from the drug. Resistance to other protease inhibitors may decrease the effectiveness of atazanavir. In some cases, particularly where resistance may be a concern, it may be necessary to boost blood levels of atazanavir by using a small dose of another protease inhibitor called ritonavir. In these cases, some of the attractive features of atazanavir are lost to some degree. Because ritonavir is known to increase lipid levels, using the combination of the two drugs will still likely lead to risks for this side effect. With this said, however, it's likely that lipid problems will be less of a concern with this boosting regimen compared to other ritonavir-boosted regimens where the second drug may also have this side effect concern (e.g., ritonavir+indinavir, Kaletra, etc.).

Increasingly, data suggests that atazanavir use in third line or salvage situations will require ritonavir boosting. In this situation the combination of atazanvir and ritonavir may be equally potent to Kaletra (lopinavir+ritonavir) and have fewer lipid-related side effects, less associated diarrhea, but higher risks for increased bilirubin and possibly jaundice. ■

Bottom Line on the Three New Drugs

Enfuvirtide (T-20, Fuzeon)

- Enfuvirtide is an injectable anti-HIV drug approved by the FDA 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.

Atazanavir (Reyataz)

- The new protease inhibitor is designed for once daily dosing; its ease of use provides an intriguing option for part of a first line regimen. When boosted with a small amount of ritonavir it may provide an additional tool in the arsenal for third line therapy.
- There are many potential drug interactions with atazanavir, and people are encouraged to pay particular attention to these when adding this drug to their regimen.

Emtricitabine (FTC, Emtriva)

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

Facial and Limb Fat Loss: Lipoatrophy

Since the advent of potent anti-HIV therapy there have been increas-ing reports of changes in body composition among people living with HIV. These include increases in fat in various areas of the body (the stomach area, behind the base of the neck and/or breast enlargement) or decreases in body fat (in the face, arms and/or legs) and changes in the way the body processes fats (called *lipids*). Any combination of these conditions is called lipo*dystrophy*. While all these conditions have been lumped together, it's likely they are actually different syndromes which are caused by different things.

Protease inhibitors and the NRTI drug 3TC are more associated with increases in lipids and/or accumulation of body fat. NRTI drugs like AZT and particularly d4T and other similar drugs are more associated with fat loss (sometimes called facial and limb wasting or lipo*atrophy*). This article focuses on lipo*atrophy*, what is known and what can be done about it.

What causes lipoatrophy?

Lipoatrophy is believed to be caused by long-term HIV infection or as a result of taking certain anti-HIV drugs. Exactly how HIV or medications to treat HIV causes fat loss remains unknown, though some suspect damage to the energy source of cells (called mitochondria) may play a role. Use of NRTI drugs are more associated with lipoatrophy. Specific drugs may be particular culprits, such as d4T, ddI and ddC (the *"d" drugs*). Lipoatrophy appears to affect White men more than women and African Americans.

What can be done about lipoatrophy?

Many questions remain about lipoatrophy, how to avoid it and how to treat it if it should occur. They include:

- Can it be avoided by not using the anti-HIV medications believed to cause it?
- Can it be reversed once it has started?
- Are there benefits to switching anti-HIV therapies or taking structured therapy interruptions?
- Can cosmetic surgery (implants or injections) provide immediate, short-term or long-lasting solutions?

The answers to these questions are taking shape as research provides clues.

Can lipodystrophy be avoided through choice of meds?

The evidence so far hints that lipoatrophy develops either slowly or more quickly depending on the choice of anti-HIV medications. Fat loss may be more rapid and noticeable with d4T, somewhat slower with ddC and ddI, but still possible with any NRTI combination. Several studies strongly suggest that combining *d-drugs* can lead to faster, more extensive lipoatrophy.

One study comparing d4T, efavirenz and 3TC with tenofovir, efavirenz and 3TC showed that the people on tenofovir had on average six pounds more fat than people who took d4T. The people who took the tenofovir regimen also had larger amounts of fat just beneath the skin (called *subcutaneous fat*) in their arms and legs than did the d4T group after 96 weeks (about two years).

It may be possible to decrease your risk of lipoatrophy by avoiding *d-drugs* in your regimen, but decreased risk certainly doesn't mean no risk. Lipoatrophy has been seen in people on a wide variety of anti-HIV drug regimens, including those not containing *d-drugs* as well as among people who have never taken medication at all.

The newly approved HIV medications emtricitabine and atazanavir do not appear to induce lipoatrophy in studies performed to date so reliance on *d-drugs* is not an automatic necessity. There is no perfect anti-HIV drug, but a very good drug not only controls HIV levels, it should also have few side effects that interfere with the quality of daily life.

Will switching therapies help once I have lipoatrophy?

Switching from a *d-drug* regimen may produce a gain in layers of fat just beneath the skin (when measured with sophisticated instruments), but this gain is often not obvious to a person when they look in a mirror.

One study found a difference in subcutaneous fat gain measurements (DEXA and CT scans) at one-year intervals for 61 people who switched from NRTI-containing regimens to ritonavir+indinavir+efavirenz. However, when asked to rate their fat gain in questionnaires, they did not personally notice any improvements.

In a study called MITOX, the half of the 111 volunteers with moderate to severe lipoatrophy who switched from AZT or d4T to abacavir (300mg twice a day) without changing the rest of their regimens also experienced about a 10% gain in subcutaneous fat, but did not notice their gains in the mirror. The other half of the group, who remained on their original regimens, saw no fat gains, either on test results or in the mirror. The measurements of fat gain were made over a six-month period, possibly too short a time to produce visible changes.

Two-year follow up results of the MITOX Study were presented at a Lipodystrophy Workshop in July of this year. Those who switched from AZT or d4T to abacavir had continuous limb fat gain (36% more fat). At this rate of recovery, researchers project that full fat stores would be restored after six years.

At the current time, the bottom line is that switching from therapies that may be causing lipoatrophy might have some benefit, but it may require considerable patience, possibly years, to see visible fat

gains. Not everyone who switches, however, will experience fat gains in the short or the long-term, as the drugs may not be the only cause of lipoatrophy.

What about injections or implants?

A variety of proven and unproven cosmetic procedures have been tried to treat facial wasting. In general, these approaches can be divided into short-term or longer-term solutions. Short-term solutions often involve injecting materials under the skin, which may dissolve and be absorbed by the body. Longer-term solutions include more permanent implants of material or injections of substances that are not absorbed by the body.

Advocating for changes

It is particularly important to recognize that unwanted facial fat loss may have a powerful psychological impact on both adherence and self-image, and can be a significant barrier to people starting anti-HIV therapy. People who are confident of their medications are more able to take them faithfully than people who fear their effects.

Facial restoration procedures are considered cosmetic and are not covered by insurance. Some women who have had radical mastectomies have seen insurance reimbursement; arguments for reimbursement for facial reconstruction are therefore possible based on prior practices. Nelson Vergel at the AIDS advocacy organization PoWer can be contacted through *www.facialwasting.org* or by phone at 713-520-6630 for information about advocacy efforts to see insurance reimbursement for facial wasting corrective procedures. For more information on lipoatrophy, call Project Inform's Hotline. ■

Other Resources

A review of cosmetic approaches for treating facial wasting is available on the Internet at *www.FacialWasting.org*.

Short-TermSolutions

Collagens (Zyderm, Zyplast, Resoplast) and hyaluronic acid products (Restylane, Perlane, Macrolane) are biodegradable and their benefits can disappear over time. Costs range from $250–500 and many are not FDA-approved. Some are only available outside the U.S. Collagen removed from one's own skin can be harvested and re-injected for anywhere from $1,000–4,000. Private insurance coverage does not extend to these procedures nor does Medicare/Medicaid reimburse for them.

Liposuction of fat from one body area to relocate the fat in facial creases is another option, but this fat may be quickly reabsorbed or migrate away from the facial area.

Longer-Term Solutions

A group of collagen implants made from tissue of dead people (Dermalogen, Fascian, AlloDerm, Cymetra) may be grafted into folds and deep wrinkles. These implants may help induce collagen to collect around the implant to render the augmentation more permanent than other collagens, which are derived from animal tissue. They are also more expensive, running into thousands of dollars. Soft implants made of man-made materials such as Goretex, Fibrel and Dermalogen are other longer-term solutions. In both these cases the body can reject the implants. Solid cheek implants of silicone or Goretex fibers should be used with caution, since they may show through the skin if the loss of facial fat is too pronounced.

Silicone gels and oils are not dissolved and absorbed by the body, but are known to relocate. They also involve risks of ongoing and visible inflammation (called *granulomas*). Silicone gels and oils lack FDA approval for facial wasting. However, LIS (liquid injectable silicone) and Silikon-1000 (microspheres of polymers) have been used at a physician's prerogative with some success, particularly when granuloma formation is closely monitored and infections are promptly treated to avoid scarring. Bioform (a polysaccharide gel) and BioAlcamid (polyalkylamide gel) are other man-made preparations that could be used for correcting facial changes. Costs average around $4,000, and often require traveling outside the U.S. to obtain the products.

A skin (dermal) graft involves taking skin from another area of the body and tailoring it to restore facial fullness is another surgical option. Facelifts vary widely in cost and effect, and can provide a long-term solution for changes from lipoatrophy.

Teflon paste and bioplastics produce very problematic inflammatory reactions and serious infections and are probably poor choices.

A study of one man-made preparation, New-Fill (polylactic acid), for facial wasting is underway at Blue Pacific Aesthetic Medical Group in Hermosa Beach, CA. Up to six treatments are done at three-month intervals; six-month and twelve-month follow ups are planned. They can be contacted by phone at 310-374-0347 or online at *www.bpacific.com*. Conant Medical Group in San Francisco is also planning a study of New-Fill; contact Chris Eden at 415-255-0744.

New-Fill can be obtained at the same price range as BioAlcamid and Bioform, and is available through DAAIR, Direct Access Alternative Information Resources at 119 West 23rd Street, Suite #404, New York, New York 10011; call 212-255-9280, fax 212-255-9355, or email *info@daair.org*. Use of this product is supported by positive reports at the 2000 International Workshop on Adverse Drug Reactions in Lipodystrophy and HIV and at the Second European Workshop on Lipodystrophy. ■

Interfering with RNA: Kill the Messenger

A number of scientific papers were published in 2002 describing the discovery of a process called *RNA interference*, or *RNAi*. The newly discovered process, whereby small strands of RNA can block the development of new genetic material, was called the "breakthrough of the year" in 2002 by *Science* magazine. RNAi has excited AIDS researchers because it has both short- and long-term potential for significantly improving the treatment of HIV disease.

In the longer term, scientists believe we may one day be able to deliver these small bits of RNA into cells in order to stop HIV from reproducing. Some scientists feel that we may also be able to intervene in the short-term, by stopping our own CD4+ cells from producing a surface receptor that HIV requires in order to infect these cells. RNAi therapy holds promise not only for treating HIV disease, but also for common infections like hepatitis B and C. Early results from treating hepatitis in animals have been encouraging.

HIV uses proteins on the surface of immune cells, like *CCR5*, in order to infect the cell. RNAi therapy aimed at blocking this process would target the gene in an immune system cell responsible for making CCR5. In this case, the RNAi therapy sends a "fake" gene that exactly matches the targeted CCR5 gene. When the CCR5 gene starts making the CCR5 protein, it also creates a set of instructions called *messenger RNA* or *mRNA*. RNAi attaches to and silences the *mRNA* before the message can be received. Once the message is silenced, RNAi seeks out more *mRNA* and silences more messages, stopping the production of more CCR5. As a result, an important protein that HIV needs is not produced, severely crippling its ability to infect a cell.

CCR5 is considered a prime target for RNAi therapy because, so far, its absence has no apparent effect on human health. Eliminating CCR5 may decrease the number of cells that HIV could get into with hopefully no serious side effects for the person. In one recently reported lab study, HIV activity in an immune cell called a *macrophage* was silenced by RNAi therapy for up to three weeks.

RNAi therapy that is designed to stop reproduction of HIV once it gets inside cells will require that the "fake" gene exactly match the HIV gene that it targets for silencing. Because HIV makes inexact copies of itself (*mutates*) each time it reproduces, targeting HIV genes directly with RNAi might be challenging. It may be prone to the same kind of resistance problems that are seen with anti-HIV drugs. However, in lab studies, RNAi aimed at HIV genes can readily block HIV reproduction.

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Messenger RNA made by any HIV gene is also a possible target for RNAi therapy. Experiments have shown that the *tat*, *rev*, *gag* and *pol* genes in HIV are all possible targets. RNAi appears to thrive for a long time and can continue targeting virus over and over. In test tubes, one treatment can produce results lasting up to ten days.

Pioneering research has produced the first successful RNAi treatment of a viral disease in a living animal: hepatitis in mice. Judy Lieberman, MD, and her team silenced the *fas* gene that is involved in nearly all types of hepatitis. This gave protection from liver cell death (*cirrhosis*) for up to ten days after a single treatment. The *fas* gene triggers cell death. So, turning off the *fas* gene and stopping cell death meant survival for mice with hepatitis. The untreated mice died of hepatitis within three days, while 82% of the mice treated with RNAi survived with normal livers. Their liver cells were protected for ten days. The effect of the treatment began to wear off after 14 days and disappeared after 21 days.

Challenges still remain as RNAi research moves from mice to man. Finding the right genes to target is critical. How to get RNAi to the cells where they need to target remains unanswered. Also, the short- and long-term side effects of RNAi therapy are largely unknown, but they probably carry some of the same concerns as other gene therapy. Those include risks of abnormal cell growth (cancer) and the methods (often viruses) that are used to get genes into cells.

The possible benefits of treating HIV with RNAi therapy offers hope. The suspected long-lasting effects of RNAi could decrease the daily demands of anti-HIV therapy. While using RNAi therapy to target HIV genes will likely be researched at first together with anti-HIV drugs, it's possible to imagine a once- or twice-a-month therapy as the new (or only) drug in your regimen.

Also, RNAi therapy may offer protection in HIV-infected cells that are not actively making virus. These are believed to be reservoirs for HIV infection. If or when these

PI Perspective

PI Perspective provides comprehensive information from the most recent studies plus perceptive analysis in state of the art AIDS treatment and research.

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cells begin producing HIV again, the RNAi already present in the bloodstream should immediately target and shut down HIV reproduction.

Aiming RNAi therapy at the genes of a virus is unlikely to create toxic side effects, since those genes do not create products that are necessary for a person to live. And because there are many possible targets for RNAi—perhaps all HIV genes at once—strategies with more than one RNAi approach could shut down HIV activity for long periods.

It is likely that hepatitis B and C will be early targets for RNAi therapy, given the direction of the research. As well, tuberculosis and other opportunistic infections may be among its next targets. It's too early to throw out the anti-HIV drugs, but the pipeline of new anti-HIV strategies has just gotten fuller. Human studies of RNAi are expected to begin in the next two to three years. ■

Interleukin-2: SILCAAT Study to Continue

In late 2002, Chiron Corporation announced its decision to shut down a large pivotal study of the drug, interleukin-2 (IL-2, Proleukin). In the days and weeks following the announcement, researchers and community activists met with the company to negotiate for the SILCAAT study to continue. In February 2003, heroic efforts by non-Chiron scientists to continue this important study were successful, and a transition of the study from Chiron into independent hands was completed. The study will continue.

For the nearly 2,000 volunteers in SILCAAT, there have been a few changes in how the study is conducted. Some minor changes have been made in the study.

What's perhaps most important to note is that Chiron's decision to stop SILCAAT was not a *scientific* decision, but rather a *business* decision. Typically decisions about stopping a study happen because the study is unable to answer the scientific question it set out to answer or because one of the study groups is doing markedly better or worse than the other(s). To the contrary in this instance, the study is in mid-stride and progressing toward answering the question in the expected timeframe. It's extremely unusual for a company to stop when everything is proceeding as planned and expected.

Bluntly, Chiron simply didn't want to pay for the study and used people living with HIV and the importance of this research question as a financial pawn. At the end of the day, Chiron will continue to provide some greatly reduced funding to enable the project to continue. The task of running the study and managing the information has been turned over to independent investigators.

This certainly doesn't make Chiron any great hero. Their business decision to pull support from this study is an affront to people living with HIV at best, and morally corrupt at worst. In facing perhaps the greatest plague in human history, Chiron leadership turned its back. Particular kudos goes to Dr. Jim Neaton at the University of Minnesota and Dr. Cliff Lane at the National Institutes of Health for their leadership in ensuring that SILCAAT continues. ■

The Basic Message

- Learn about HIV testing options and choose one that fits your needs! Be sure your privacy is protected!
- If you're positive, don't panic. If you make your health a priority, chances are you will be reasonably healthy for many years.
- Learn about your healthcare options and local support services.
- Get a complete physical and blood tests for CD4+ cell count and HIV level. Repeat quarterly and watch for trends. Women should get GYN exams and Pap tests every six months, more often if abnormal.
- Work with a doctor to develop a long-term strategy for managing HIV disease.
- If the CD4+ cell count is below 350 or falling rapidly, consider starting anti-HIV therapy. Test at least twice before taking action.
- If anti-HIV therapy fails to reduce your HIV level below the "limit of detection" or below 5,000 copies within 3–6 months, consider a different or more aggressive therapy.
- If the CD4+ count trend stays below 300, consider treatment for preventing PCP. If it stays below 200, start treatment for preventing PCP (if you haven't already done so) and reconsider anti-HIV therapy if not on one. Learn about drug interactions and preventive treatments for opportunistic infections.
- If you started preventive therapies and your CD4+ cell count rises in response to anti-HIV therapy, ask your doctor whether it might be safe to stop certain preventive therapies.
- If your CD4+ cell count stays below 75, consider more frequent blood work—perhaps monthly. Consider therapies for preventing MAC/MAI and CMV.
- Regularly seek support for your personal, spiritual and emotional needs. It takes more than medicines to keep you well.

Sex, Gender and HIV

There is an ongoing dialogue within HIV research about how HIV affects men and women differently and how they may respond to therapy differently. What is often overlooked is the difference between sex and gender. Sex is based in a person's biology. Gender is based in how society treats men and women because of their sex and how their roles and responsibilities are generally ascribed to them. Sex and gender may play a role in the differences seen between men and women living with HIV. So what are these differences and how do they impact the course of HIV in men and women? This article will attempt to answer some of these questions.

Sex and gender: What's the difference?

Sex is biological, referring to the makeup of a person's body. Gender is socially defined, referring more to the roles that men and women play in society. It's unlikely that there are differences in a person's ability to stay on a medication regimen based on sex. There's likely nothing biologic that makes it more or less difficult for a woman to take her medications once, twice or three times daily. However, gender may play a big role in impacting adherence. Together, sex and gender create unique experiences for men and women living with HIV.

Impact on HIV and response to treatment

Over the past several years, there have been discussions about how HIV disease develops in women and men. Research has shown sex differences in viral load. During acute/early infection, women tend to have lower viral loads than men with the same or similar CD4+ cell counts. However, this difference appears to remain only in the first three to five years of infection. No impact has been seen on disease progression overall.

This lower viral load does not put women at either lesser or greater risk for disease progression. To the contrary, most studies suggest that men and women progress from HIV infection to symptoms of AIDS at similar rates over time. Some studies even suggest that women may actually live a bit longer, and thrive better, with HIV disease. The cause and significance of viral load differences remain unclear, although one explanation is the role of the female hormones, estrogen and progesterone. Sex hormones in women can interact with HIV.

Currently, differences in viral load have not warranted different approaches to treating men and women with HIV. Although these differences are highlighted in the Federal Guidelines, the Guidelines Committee did not conclude that women should consider starting anti-HIV therapy at lower viral loads.

Sex hormones may also affect parts of the immune system, such as the presence of proteins on cells called chemokine receptors. These proteins are used by HIV to infect a cell. One example is the CCR5 receptor. The greater the number of CCR5 receptors on the cell, the more proteins HIV can use to infect the cell. This makes it easier for HIV to enter the cell, begin to reproduce and move on to infect and destroy more cells.

In general, the amount of CCR5 on a given cell is less in women than in men. Research shows that progesterone can affect the amount of CCR5 receptors. The lower the levels of progesterone, the fewer CCR5 proteins are on the cell; the higher the level, the more CCR5 proteins are found.

Interpreting these differences between men and women is difficult. There are many possible conclusions but not many hard and fast answers. Based on what we know, we could conclude that lower viral load in early infection would lessen a woman's risk for HIV disease progression. Also, having lower levels of CCR5 on immune cells, in theory, should also lessen her risk. Yet studies show that women and men have similar courses of HIV disease. It's possible, as with other diseases, that woman's bodies are more capable of fighting HIV infection over time.

Sex and response to therapy

Most studies show that women and men respond equally well to anti-HIV therapy. A few suggest that women may actually respond better and are less likely to experience disease progression. However, there are confounders in these studies that don't really provide a clear picture about using anti-HIV therapy among women. The good news is that there don't appear to be sex differences in the way men and women benefit from therapy. Gender, however, may well play a role in how and whether women benefit equally.

Sex and HIV-related complications and side effects

Women may experience different complications related to HIV disease and different side effects from taking medicines. These differences have sometimes been attributed to factors such as sex hormones.

Some research has noted that sex differences in how the body processes and clears a drug can be related to the levels of sex-specific hormones. However, a woman's biology impacts the way she processes and clears drugs from her body. In general, a woman's average body weight is lower than a man's, yet women have more body fat. Body weight and the amount of body fat influences the amount of drug distributed in the body and the rate it clears from the body. What this means for women is that they may face an increase in specific side effects while on therapy.

With the exception of some gynecological conditions, it is rare to find side effects unique to women. When taking ritonavir, women sometimes experience abnormal

menstrual cycles. In all other cases, women might have certain side effects associated with a drug more often or severely than men, but in general there are not side effects that are different or unique to women.

Women, particularly overweight women, appear to be more likely to experience fatty liver (*hepatic steatosis*) and increases in lactic acid (*lactic acidosis*), related to NRTIs. The risk for severe (and possibly fatal) lactic acidosis appears to be greater among pregnant women who take both d4T and ddI. Inflammation of the pancreas (*pancreatitis*) may also be more common in women.

While both women and men might experience a rash as a side effect of nevirapine, women appear to be slightly more at risk for it. When the rash does occur in women, it's more likely to be severe.

Changes in body composition (lipodystrophy) occur in both men and women. However, data suggest that women may be more at risk for this complication. Women are more likely to experience breast enlargement than men and are more likely to face changes in the way fat accumulates (lipohypertrophy). Interestingly, in the general population regardless of HIV infection, women appear to experience lipodystrophy more often than men.

Recent data from the FRAM (Fat Redistribution and Metabolic Change in HIV study) reported that HIV positive women in the study had higher triglyceride levels than HIV negative women in the study. The study also reported that HIV positive women enrolled had the most fat loss in the legs. (See article on lipoatrophy on page 11.)

The level of sex hormones, namely progesterone and estrogen, can cause drug interactions with anti-HIV therapy. For instance, specific protease inhibitors can affect the levels of estrogen or progesterone in oral contraceptives. These interactions can impair how effective the anti-HIV drugs are. People can lessen their risks for drug interactions by working with their doctors or pharmacists and letting them know all the medications they're taking—prescription, over-the-counter, recreational drugs and alternative medicines. Changing doses may be necessary.

In terms of differences in HIV disease, women experience gynecological (GYN) complications. These are often the first sign and symptom of immune dysfunction when women may suspect and test for HIV infection. Women living with HIV may experience many GYN conditions that can be more severe and less responsive to treatment than in HIV-negative women. These can range from recurrent vaginal yeast infections to aggressive vaginal warts and cervical cancer. (For more information on GYN conditions, call Project Inform's Hotline.) Women who experience wasting syndrome (extreme weight loss accompanied by loss of lean muscle) are more likely to lose fat tissue, whereas men are more likely to lose lean muscle tissue. Also, women are less likely to experience oral hairy leukoplakia and the AIDS-related cancer, Kaposi's Sarcoma, than men.

Gender and HIV

Keeping in mind that gender and gender roles are socially defined, gender can affect a woman's ability to take medicines, thus her response to anti-HIV therapy. In addition, a woman's access to care and her ability to take care of her overall health are influenced by her gender and role in society.

Women may face multiple challenges and barriers when it comes to their own health and well being. Many live in domestic violence situations, experience social stigma and discrimination, lack economic security and healthcare, and are often the primary caregiver for the family. These challenges all play a tremendous role in their ability to go to the doctor, pick up medicines, take medicines, rest and maintain a low level of stress.

Conclusions

Research that looks carefully at the impact of sex on HIV and response to therapy is critical to understanding differences and taking steps for better treatment and care for women. In order for this to happen, studies must be designed to enable both the impact of sex and gender when the data are analyzed. This means having enough women in the studies. In addition, there needs to be a clear benefit for women who are interested in being a part of the research.

The following is a list of online resources that may be helpful:

Center for AIDS Research (CFAR)
www.niaid.nih.gov

Clinicaltrials.gov
www.clinicaltrials.gov

TrialScope
http://hivinsite.ucsf.edu/tscope

American Foundation for AIDS Research
www.amfar.org

Adult AIDS Clinical Trials Group
http://aactg.s-3.com

Perhaps the best news from the research to date is that women live as long and maybe even longer than men with HIV. Women have biological factors that may enable their immune systems to better resist HIV infection. Women appear to benefit equally well from therapy, and some research suggests they may actually do better. The messages that women do worse, die faster or don't benefit from anti-HIV therapy have pervaded for far too long and simply aren't supported by research. Women have been done a great disservice to be given these messages of despair and hopelessness.

To simply know there are differences between men and women is not enough. We need to better understand why they exist so that we can develop proper interventions. In addition, it's important to be aware of the factors that can influence a woman's ability to take care of her health. From this place we can develop better treatment and care strategies that take into account both the sex and gender of women living with HIV. ■