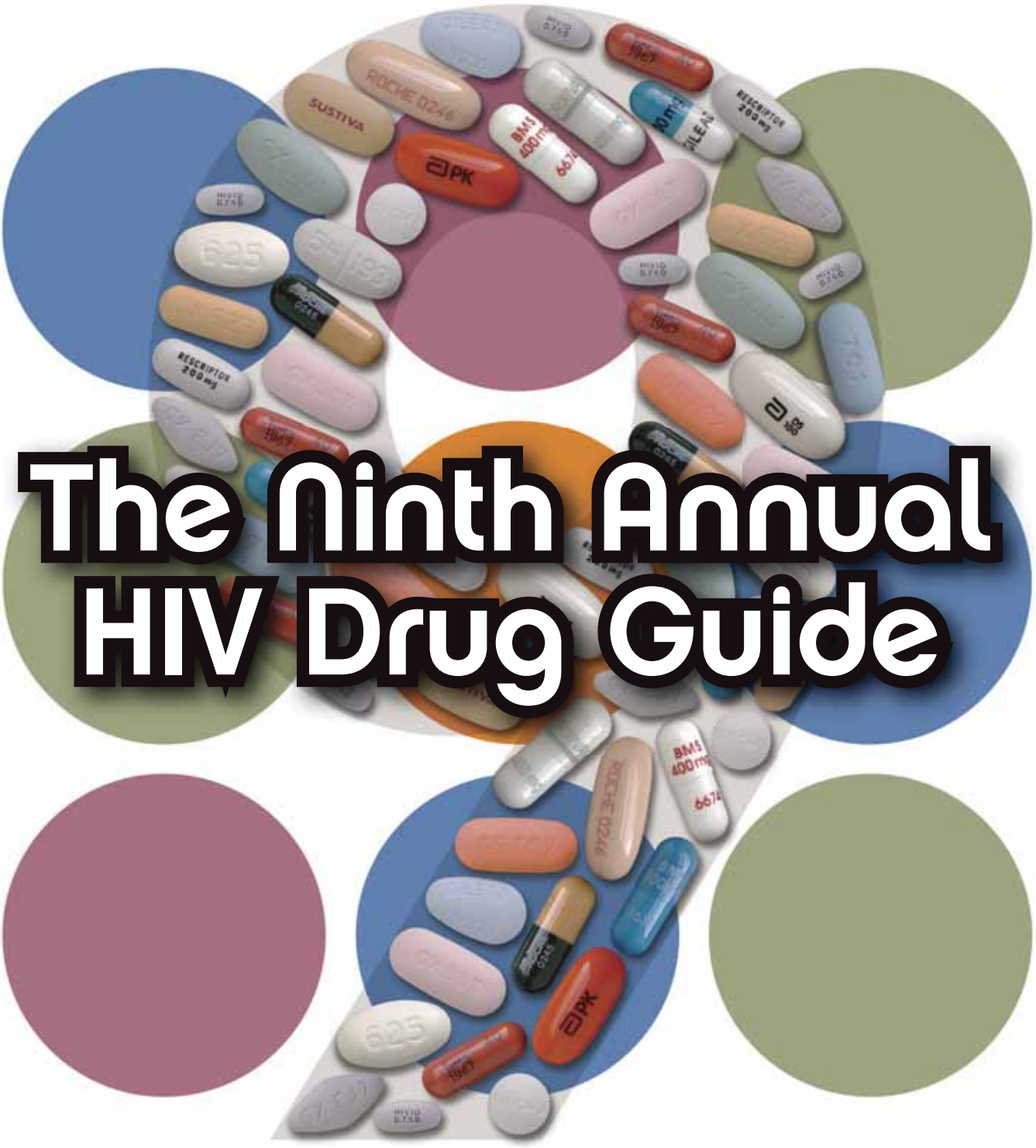
January / February 2005

Positively Aware

The Journal of Test Positive Aware Network




# The Ninth Annual HIV Drug Guide

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A model, photograph, or author's HIV status should not be assumed based on their appearance in *Positively Aware*.

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January / February 2005
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## Articles





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Distribution of *Positively Aware* is supported in part through grants from the AIDS Foundation of Chicago, Illinois Department of Public Health, GlaxoSmithKline and Abbott Laboratories.

# Position Available: Executive Director

Test Positive Aware Network is a leading HIV-related service organization in Chicago, and the publisher of two national HIV/AIDS treatment journals, Positively Aware, and Positively Aware en Español. We are seeking a suitably qualified person to administer the agency, including program development and management, fiscal and staff management, public relations, fundraising and board relations.

Test Positive Aware Network empowers people living with HIV through peer-led programming, support services, information dissemination, and advocacy. We also provide services to the broader community to increase HIV knowledge and sensitivity, and to reduce the risk of infection. Our client base is diverse across racial, ethnic, gender, gender-identification and economic lines.

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# Winners and Losers

A little over a month ago, I phoned my doctor's office to schedule an appointment to have my labs done. I've been on a combination of Sustiva plus Kaletra for three years, and have remained undetectable with a T-cell count in the near-normal range, and a high CD4 percentage. I'm way beyond "third-line" therapy, this is probably easily "sixth" or "seventh" line for me, but who's counting?

Crixivan was my first protease inhibitor, and almost immediately I went to undetectable, and my T-cells turned around and started to increase gradually after having steadily declined for years. Suddenly, I thought, "Maybe I'm going to beat this thing". The food restrictions on un-boosted Crixivan were nearly impossible, and yet I figured out how to adjust my lifestyle to take it three times a day on an empty stomach, eight hours apart, and drink copious amounts of water. I learned to live with it.

And then all it took was one street fair, throw in a little too much sun, a couple of beers and not enough water, and voila: "Crix" stones, which were so painful that I ended up being hospitalized. I was crushed when my doctor told me I had to stop the drug. But pain is a great motivator, and so I agreed to switch to the next best thing at the time, Viracept.

Thus I traded one side effect for another, this time enduring frequent and excessive diarrhea for several years, and, not surprisingly, after a while my viral load broke through, and slowly began to rise. But then it stabilized around 1,000, and my immune system remained intact. So we watched, and we waited, because at the time there weren't a whole lot of other options. And remember the first formulation? Five chalky pills that got stuck in your throat every time you tried to swallow them, twice a day? Yuck! But, again, I learned to live with it.

Fast-forward several years later: My viral load started climbing, and my T-cells had begun their gradual decline once again, like troops of soldiers valiantly marching to certain death. A resistance test confirmed our worst fears: the dreaded D30N mutation, which is associated with Viracept resistance. And I began to see the effects of lipodystrophy. Was it brought on by the years on AZT, then Zerit, was it the mitochondrial toxicity, or the protease inhibitors, or all of the above? Maybe it was the virus itself that caused my face to begin caving in. Or was it because I am an HIV-positive white man over 40? Who could say for sure?

After careful thought and consideration, my doctor and I decided to pull out the big guns: Kaletra plus Sustiva. The plan was, let's get back to undetectable, restore my immune system, and knock the crap out of this virus. I had been on Viramune for about a month several years earlier, but I didn't respond to it well, so I switched off right away. While a resistance test now didn't present with the typical non-nuke mutations, it probably wouldn't have anyway, since I hadn't been on the drug for quite a while. So it was a gamble to go with another non-nuke, which I could be resistant to, but one I was willing to take.

So back to the future, here I am, I have 905 T-cells, my CD4 percentage is 30%, and my virus is undetectable. Kaletra and Sustiva had lived up to their promise, even exceeding my wildest expectations. I had a new lease on life. Aside from that first couple of days on Sustiva, when I felt like I was on a mix of qualuudes and downers, and other than a few really bad nightmares now and then, I actually started to enjoy the "vivid" dreams, and Immodium is my new best friend. I'd learned to live with it once again.

I quit smoking over seven months ago, I've been taking better care of myself, watching my diet, and back at the gym 3-4 days a week, back up to my ideal weight, and feel and look better than I have in a long time. So what's wrong with this picture?

Well, my labs from the doctor raised a few flags. My cholesterol, while not ideal, was "okay" at 213 (normal is under 200). It was my triglycerides that had gone through the roof, at 965. We always knew that this was a distinct possibility, if not highly probable, with my current combination. But it had been three years without a hitch, so I thought I was home-free.

Life with HIV is like being part of a professional sports team. You're the owner. Your doctor is your coach. The meds are your players. At the end of the season, you make high profile deals and trades. Sometimes you take a gamble on a new player, sometimes you stick with the tried and true, even when they're not performing at their best. Some coaches focus more on offense, others on defense. And sometimes you have to break up a winning team.

My players have decided they want to renegotiate their contract. If we want to see them back next year, we're going to have to pay.

So we brought in a mediator. Enter Lipitor. He doesn't have the stature and the star-power of Kaletra or Sustiva, in fact, he's

just a little guy. He's not even in the same league. But guess what? It's working: my total cholesterol is down to 160, triglycerides are at 475, and liver functions are normal. I can't wait to see what next season brings.

I'd like to thank the players for this season's winning team in helping with the Drug Guide: Enid Vázquez, without whom this year's Drug Guide would have been nearly impossible; Russell McGonagle for making the magazine come to life on the page; Ross Slotten, MD, for everything you do—thanks, doc; Tony Hosey, PharmD at StatScript for the skinny on the drugs; Heidi M. Nass for your insightful look at the flip side; Keith Green for putting together the index; Matt Sharp; Patrick G. Clay, PharmD; Andrew Halbur, RPh, at Walgreens; and last but not least, Dr. Dan Berger for your invaluable contributions over the years.

Jeff Berry
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John is a 45-year-old man who recently learned that he is HIV positive. He has a CD4 count of 350 cells and a viral load of 60,000 copies. What should he do?

Despite two decades of intensive research, the publication of hundreds, if not thousands, of studies in respected journals, and the development of treatment guidelines by a panel of experts in HIV disease, there is no best answer. In fact, if John consults ten physicians specializing in the treatment of HIV, he's likely to get ten somewhat different opinions about his next course of action. And they'll probably all be right.

In 2005, the management of HIV/AIDS is still more of an art than a science, no matter what the experts tell us. No two HIV positive patients are alike; and decisions about their care must be individually tailored. This will continue to be the state of things until a cure is discovered and all controversy about HIV treatment will end.

Before proceeding further, I want to emphasize two important points. First, if left untreated, 95% of people infected with HIV will die of AIDS. Second, HIV infection is a manageable problem—that is, it can now be considered a chronic disease, like diabetes (at least

# Starting treatment, staying on therapy

by Ross Slotten, MD

in the developed world). It's conceivable that a person can live a normal lifespan with his or her HIV infection as long as he or she adheres to his or her therapy.

Not enough time has passed to know if people can remain on antiretroviral therapy for 20, 30 or 40 years. However, we know that people can be treated with the same regimen successfully for at least a decade and probably for much longer. The usual reason for the failure of therapy is not the sudden ineffectiveness of the medications but patient noncompliance. It takes a lot of energy and dedication not to skip doses. Unlike diabetes, if you skip doses of your HIV meds, you can't "catch up." Doctors must be cheerleaders as well as practitioners.

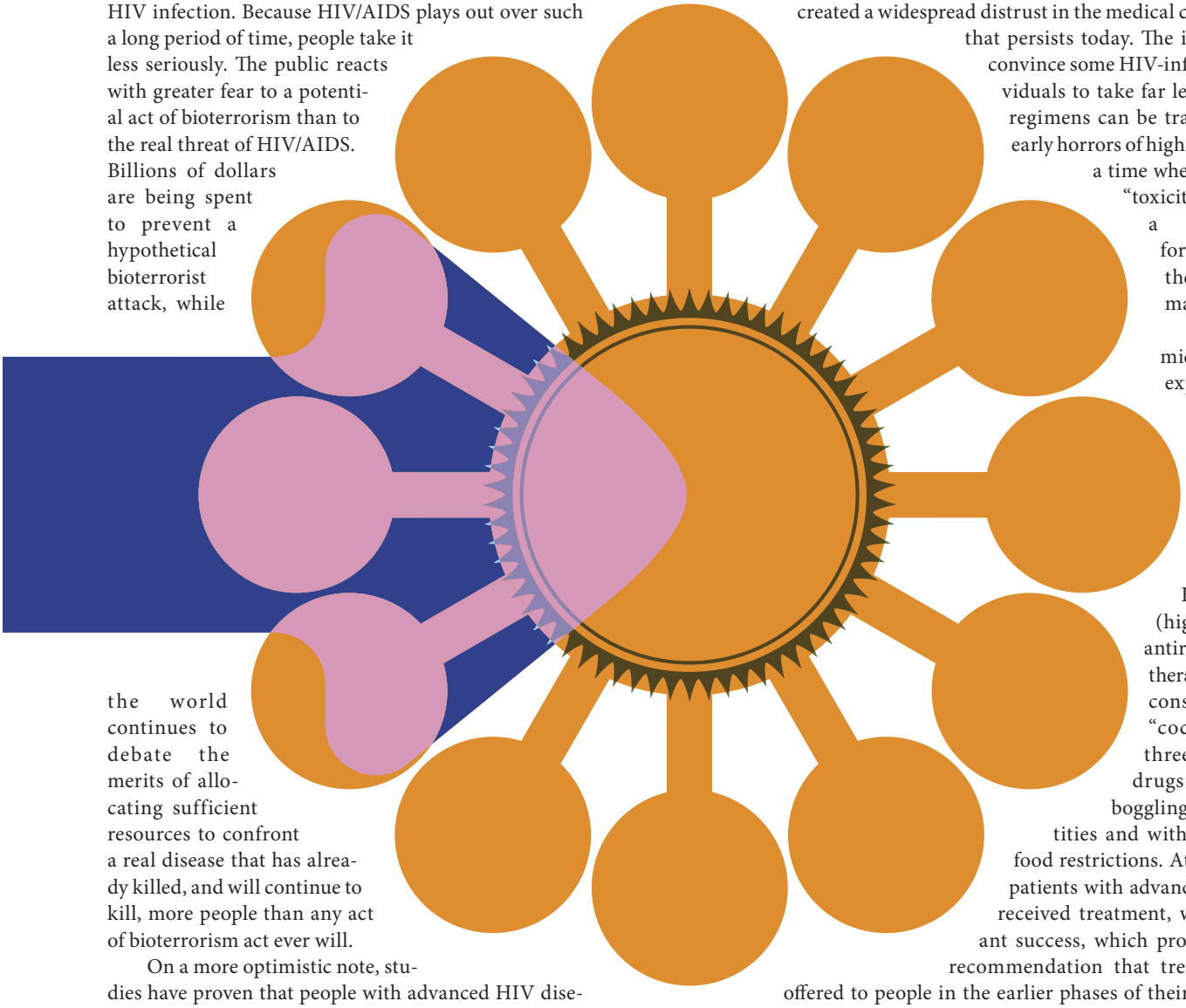
### How HIV works

Scientists have long understood the natural history of HIV infection, which has not changed since the first reports of AIDS in 1981. On average, a decade passes from the time of infection to the time of death. Some people die within one to two years of infection, others will die 15 to 20 years after being infected—it's a bell-shaped curve. But again, less than 5% of people will survive their HIV infection if untreated.

There are people who believe that because they are HIV negative despite unsafe sexual behavior they are somehow immune to HIV. This is a fallacy: we do not yet have a test to identify those with an innate resistance to the disease. One can have a single sexu-

al encounter and get infected or a hundred and not get infected. Sooner or later, the vast majority of those playing Russian roulette with the virus will get infected. Therefore, all people must consider themselves to be at risk for acquiring HIV and should take the proper precautions to avoid infection.

They should know that, except for rabies, which has a mortality rate of 98%, no other disease—not the plague, not Ebola virus, not anthrax, not smallpox—approaches the mortality rate of HIV infection. Because HIV/AIDS plays out over such a long period of time, people take it less seriously. The public reacts with greater fear to a potential act of bioterrorism than to the real threat of HIV/AIDS. Billions of dollars are being spent to prevent a hypothetical bioterrorist attack, while the world continues to debate the merits of allocating sufficient resources to confront a real disease that has already killed, and will continue to kill, more people than any act of bioterrorism act ever will.



On a more optimistic note, studies have proven that people with advanced HIV disease—those with CD4 counts well under 200 cells or with a history of an opportunistic infection like pneumocystis pneumonia or cytomegaloviral retinitis, for example—have benefited from HIV medications. We all know people who were plucked from the jaws of death and lived to tell their tales because of the timely administration of life-saving therapies. Thousands of people with CD4 counts once hovering near zero have resumed near-normal, productive lives. Yet the prospect of taking lifelong medications often terrifies people more than the prospect of death from AIDS. What have we done wrong?

### Treating HIV

The story of HIV treatment is the classic tale of hype and hope, of high expectation and inevitable disappointment. When AZT first became available in 1987, a period of darkness seemed to be ending; but the punishing schedule (two pills every four hours around the clock), the significant adverse effects (headaches, nausea and vomiting, and severe anemia requiring blood transfusions), and ultimate failure to improve life expectancy beyond a few extra months, created a widespread distrust in the medical community that persists today. The inability to convince some HIV-infected individuals to take far less noxious regimens can be traced to the early horrors of high-dose AZT, a time when the term "toxicity" became a synonym for poison in the minds of many.

In the mid-1990s, expectations were raised once again with the development of HAART (highly active antiretroviral therapy), which consisted of a "cocktail" of three different drugs in mind-boggling pill quantities and with annoying food restrictions. At first, only patients with advanced disease received treatment, with brilliant success, which prompted the recommendation that treatment be offered to people in the earlier phases of their infection, before symptoms developed. Studies soon focused on those who had just become infected: it was theorized that after only two or three years of treatment, HIV could be eradicated and a person thus cured. Hit hard and hit early became the mantra of the day.

Pressured by health professionals and AIDS activists, the insurance industry and governmental programs like ADAP (AIDS Drug Assistance Program) quickly relented and permitted access to therapy for all HIV infected individuals. No longer did ignorance of one's HIV status seem reasonable. Moreover, studies bolstered the cost-effective strategy of treating HIV infection long before the development of opportunistic infections. With greater confidence we coaxed our patients to get tested; and those who tested positive we urged to consider treatment. Even people with CD4 counts in

the normal ranges (above 500 cells) who had little likelihood of becoming ill for a decade were often prescribed HAART.

The bubble burst when researchers discovered that current treatments didn't cure HIV. The virus disappeared into hidden reservoirs that have yet to be discovered—cessation of therapy results in rebound of the virus to pretreatment levels and renewed destruction of the immune system. Far worse than this discovery, however, was the recognition of bizarre, unexpected side effects that, because of the rush to bring effective therapies to market, were not reported in clinical trials.

Some people noticed that their faces were shriveling; others complained of disfiguring deposits of fat on the backs of their necks; still others developed protuberant abdomens, skinny arms and skinny legs. Doctors also diagnosed more cases of diabetes than expected or alarming elevations of serum cholesterol and the so-called bad cholesterol, LDL. A new disorder had emerged, lipodystrophy syndrome, one that was easy to identify but hard to define because of the lack of objective criteria.

At first Crixivan, a protease inhibitor, was blamed as the cause of the syndrome ("Crix belly" it was called)—at the time, Crixivan was the most popular protease inhibitor prescribed. Soon, however, the syndrome occurred with other regimens. Today, Zerit, Videx and Retrovir, the so-called thymidine analog nucleoside reverse transcriptase inhibitors (NRTIs), have been implicated as the main culprits because of their effects on the machinery of mitochondria, microscopic bodies found in every cell. (Mitochondria are known as the cells' powerhouse because they convert food into energy.)

But by what mechanism HIV drugs cause this syndrome is still unknown. Stopping therapy or switching to another regimen doesn't reverse the syndrome. Moreover, no one can claim with absolute certainty that the syndrome won't occur with every combination of current HIV medications, even if thymidine analogs and protease inhibitors are excluded from the regimen.

Suddenly, the hit early, hit hard game plan came under fire. Patients questioned the wisdom of starting therapy so early in the course of their disease. Those already on treatment wondered if intermittent therapy might minimize long-term side effects without compromising the effectiveness of medication. A minority failed to recognize any benefit of HIV treatment, preferring to take their chances and hold out for therapies with far fewer adverse effects rather than suffer permanent disfigurement and impaired quality of life.

### What next?

As always, scientists and physicians hesitated to revise their recommendations, warning of the dire consequences of any modification in the management of HIV infection. Today, we often wait as long as possible to initiate therapy, prescribing medications when the benefits of treatment outweigh the downside of treatment. As the CD4 count approaches 200 cells, the risk of developing an HIV-related problem increases; and the higher the viral load, the faster that person will reach that 200 CD4 count. A person with a viral load of 100,000 will get sicker faster than a person with a viral load of 2,000.

So, what can we advise John to do? He should probably repeat his CD4 count and viral load before making any decision. However, let's assume that he gets similar results. He has four options. According to the NIH guidelines for using antiretroviral agents among HIV-infected adults and adolescents, he could begin therapy now because he has a greater than 60% chance of progressing to AIDS in the next three years. Once he has started medications, he should consider his treatment to be lifelong.

On the other hand, he has a 40% chance of not progressing to AIDS in the next three years; and, with a CD4 count well above 200 cells, he's not in any immediate danger. Therefore, he could opt to monitor his CD4 counts and viral levels closely until he feels that it's no longer prudent to wait.

Third, if the opportunity is available to him, he could enroll in the SMART trial, an international trial funded by the NIH and conducted jointly with community-based HIV medical practices. In this study, patients with CD4 counts of 350 or above are randomized to one of two groups: group one, in which patients begin standard anti-HIV therapy as soon as they enroll in the study, no matter how high their CD4 count; and group two, in which patients delay therapy until their CD4 count drops to 250. Those assigned to the latter group take their medications until their CD4 counts rise above 350, at which point they stop their therapy, resuming when their counts drop back down to 250. This study hopes to answer the following questions. Is their any disadvantage to delaying therapy until a near-AIDS level CD4 count? Is their any advantage to intermittent therapy—that is, do patients who interrupt their therapy have fewer side effects but the same long-term benefits as those who remain on indefinite treatment?

A final option for John is to do nothing and avoid doctors until he becomes ill. A fraction of patients are so fearful of medications and doctors that they evade the health care system until they've developed an opportunistic infection. Although many opportunistic infections are treatable, some are not; or multiple infections may develop in a single individual, leading to prolonged hospitalization and complex treatment regimens with horrible side effects; or the patient may die during the course of treatment. Few doctors or patients would choose this course.

However, if John fits this patient description, he might be better off delaying his therapy until the last possible moment rather than risking the development of multiple drug resistance because of poor compliance. Sometimes it takes a brush with death to convince a person to treat his or her HIV infection.

For the majority of people, however, it's not "if" he or she will be treated but "when." Unlike people with other life-threatening diseases like cancer, who must undergo treatment as soon as possible, those with HIV infection usually have months or years to ponder their options, jointly deciding with their doctors not only when to start treatment but also what particular regimen will work best for them.

*Ross Slotten, M.D., M.P.H., is a board certified family practitioner in Chicago who has been caring for people with HIV since 1981. His three-physician group, Klein and Slotten Medical Associates, treats mainly gay men and is among the largest private HIV practices in the Midwest. He is currently a consultant for AEGIS, the biggest free-access HIV/AIDS knowledge base on the web. Since 1989, he has been a member of CPCRA (Community Programs for Clinical Research on AIDS), a community-based national clinical trial network sponsored by the National Institutes of Health. Dr. Slotten can be reached at rslotten@aol.com or 1-312-280-0996.*

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# My Meantime Blues

*by Heidi M. Nass*

Recently I was asked to write a short, basic piece about the status of HIV treatment for a local newsletter in Madison. I wrote about how many drugs were available, but that some of them are too alike or too toxic to be useful, and how we urgently need new agents that work on new targets to help people with lots of viral resistance. I showed the finished piece to my boss, a dedicated and skilled HIV physician of many years, who wondered if I could make it, well, more "upbeat" I think was the word.

I realized that the different perspectives of my boss and I illustrated how one's view of this epidemic is informed by where one sits. His medical practice has gone from managing one opportunistic infection after another with fingers crossed and little else to offer, to navigating an arsenal of drugs for patients who are re-acquainting themselves with the notion of old age. And me? I live with this virus.

Clearly, there are reasons to be encouraged. Progress has been swift—we've learned an enormous amount in a relatively short time. We've gone from no weapons to fight HIV to 26 antiretroviral drugs approved in the U.S. Many of the medications approved in recent years are much easier to take than what was available just 10 years ago, which is helping people keep the virus at bay. We have a genetic map of the virus and researchers who are exploring all the places the virus might be vulnerable to attack. We are learning things about the immune system that weren't well understood before, which may show us new places to disrupt the infection and disease process.

Still, we've got troubles. HIV integrates itself into our DNA, making it difficult to flush out and eliminate—the perpetual lack of promising vaccine candidates illustrates this painfully. HIV has proven itself to be a wily opponent—prolific enough and sloppy enough to make the emergence of resistance to medications an inescapable eventuality. The continual development of new classes of antiretrovirals is the most feasible way to stay ahead of the virus.

Where science and politics intersect it gets even more worrisome. It's taken way, way too long to mobilize the political will to develop a workable microbicide that would allow continent after continent of women to protect themselves from infection. Instead, we have leaders who preach abstinence as the way of prevention in places where the single greatest risk for HIV infection is being a married, monogamous woman.

While drug companies and governments have been playing their murderous blame game with each other, AIDS has been marching across Africa, Asia and Eastern Europe, killing by the millions. Here, in the richest country on the planet, poor people die on wait lists for medications.

I want to be more, um, "upbeat"—I do. It's just hard to reconcile a sunny outlook with what I see around me. In recent years, the U.S. rates of HIV infection and AIDS diagnosis have increased. Meanwhile, after dropping 70% between 1995 and 2002, the AIDS death rate has stopped falling. Our community of treatment advocates keeps losing remarkable national activists to AIDS—Carlton Hogan of Minneapolis and Joel Martinez of Houston in the last year alone. A woman who spoke at one activist's funeral expressed the feelings that many of us share when she said, "I just feel broken."

Don't get me wrong. I'm more grateful than I could possibly express that there are extraordinary people among us who would be dead by now were it not for the progress that's been made in treating HIV. I just want treatment to advance at the speed necessary for them to stay ahead of the virus.

Talking about AIDS as a "lifelong manageable condition" seems premature, given the trickle that is our pipeline. I want pharmaceuticals to aggressively pursue development of ways to stop this virus cold instead of fine-tuning and re-packaging what they've already sold us. The current agents have shown they have an effectiveness expiration date and toxicities that may further limit their long-term use. We need committed, creative exploration of new approaches instead of recycled, take-it-to-the-bank drugs with nothing new but a fancy name.

There are 26 approved anti-HIV medications. If we subtract the ones that are just combinations of two or three drugs in one pill, and those that aren't really good for much, we're down to about 20. After we account for the fact that some cannot be used together and others are of no use to people who've been around the block with these medications, what sounds like a treasure trove of regimens is, on closer inspection, a good set of choices for someone new to ARV therapy and a dodgy selection for the rest.

There are some agents in development that work on HIV in a whole new way. If these new medications pan out, we can begin to imagine a future of treatment that looks different, and more hopeful. However, those of us living in the meantime must confront an evolving set of confusing and complicated questions and carefully craft our treatment decisions from a disjointed, dizzying landscape of data.

*Should I start treatment now or wait?* Sounds like a straightforward question but requires some careful consideration—an earlier start on antiretrovirals can suppress viral load and postpone disease progression, but it also means more exposure to toxicities and side effects and more opportunity to miss doses, which invites viral resistance and a reduction in future options. It's a delicate decision that should rightfully take into account the whole of a person's situation, not just viral load and CD4 count.

*Should I focus on what would be easiest to take or what would be the most potent?* Medications have improved but, regrettably, this choice is still real. Some medications that are more forgiving of missed doses also have more side effects and a more difficult dosing schedule. The decision is compounded by the specific viral mutations that any particular regimen invites, and the need to

consider which regimen will have the best "go-to" option if (more likely, when?) viral resistance develops.

*If my virus is suppressed but my regimen is getting harder for me to take, can I switch to something easier?* Will a new regimen have new side effects?…will it be as potent?…if I stay on my current regimen, will I start to miss doses because it makes me miserable? HIV treatment is loaded with choices between the devil we know and the devil we don't know, and this is one of them.

*If my virus is not suppressed but I'm tolerating my current medications, should I switch or stay?* People who are not suppressed on their first regimen will likely have a feasible Plan B. People who've been on various regimens with limited success have a tough decision to make and must take into account competing interests and concerns: if I maintain a viral load, will I incur deeper and deeper resistance?…if I have some virus circulating but my health is stable, dare I rock the boat by switching?…will a regimen that is potent enough to knock down resistant virus be tolerable?…should I try to hold out until there's more than one new drug (or two?) available to me? Like no other, this question divides people who are treatment-naïve from those who are treatment-experienced.

Many people never even get to these questions, as they constitute a privilege all too closely associated with race, gender and wealth. A recent observation study of 3,000 HIV-positive people in the U.S. showed that, while a modest viral load doesn't make someone more likely to get sick or die, a viral load over 20,000 copies/mL does. In the study population, those who had higher viral loads were significantly more likely to be non-white and have spent less time on antiretrovirals. This data is consistent with other studies showing that poor women, blacks and Latinos are offered antiretrovirals less often than others.

Globally, the situation is gruesome and devastating. Millions of people are dying—not because they have a fatal disease that has no treatment, but because they can't get their hands on the treatment. The failure of their governments, the pharmaceutical industry and wealthy nations to craft a solution—something that is within their joined means to do—is killing families and destroying communities around the globe.

The mediocre monetary commitment of the U.S. government to the Global Fund to Fight AIDS, Tuberculosis and Malaria falls shamefully shy of its contribution capacity as the world's wealthiest nation. In South Africa, the hardest hit country on the haedest hit continent, years were lost because the government denied that HIV is the cause of AIDS. And then there's the pharmaceutical companies.

Last year, at the first meeting on drug pricing between people living with HIV/AIDS in the developing world and representatives of international pharmaceutical companies, Roche was the bluntest of the bunch: "The fact that our drugs are not affordable in some parts of the world is not Roche's responsibility," the company representative said. Boehringer Ingelheim explained that Central America was not getting the same price for their drugs as the Caribbean, even though the regions are economically similar, because they were controlled by two different BI offices. "It is a big internal battle within the company," the representative said. "Any company has a lot of politics; and we have a lot of people who came up through the pharmaceutical industry." GlaxoSmithKline defended its practice of redefining what constitutes its "no profit" drug prices to take into account whether cheaper generics are available by saying, "You see this anywhere generics come in. We cut prices to keep a part of the market. It is a commercial practice."

Given the nature of corporate practices, the deficit of political will, the imposing scientific challenges and the dimensions of the epidemic, is it any wonder I have a hard time getting to "upbeat"?

Newly diagnosed people sometimes ask me, "Do you think we'll see a cure in our lifetime?" I can't bear to say "no"—if there's ever a time to be upbeat, it's when you're talking to someone just diagnosed with a life-threatening disease. "We'll see," is what I often say, followed by, "In the meantime, our challenge is to make the best use of what's available to us so we're in the best possible position to take advantage of whatever comes next."

My friend, Matt, said it all in an e-mail exchange we had last year during a spate of deaths in our activist community: "…after all the good news with ARVs, we are shaken to deal with the losses again. I look at the deaths as another wake up call…

It brings back the reality of my situation, and I get worried about my health. On the other hand it gives me more resolve to keep on fighting."

The truth is, the meantime is all we've got.

*Heidi M. Nass is a lawyer turned treatment educator and community advocate based in Madison, Wisconsin. She works at the University of Wisconsin HIV clinic, which serves 700 patients. She writes about HIV-related topics for various publications and is a member of the national AIDS Treatment Activists Coalition (ATAC). She has been living with HIV for 10 years. She can be reached at hmn@medicine.wisc.edu.*

# Combining the HIV Drugs

by Enid Vázquez


It's nice to look at the HIV drugs separately, but in the real world, the meds must be taken in combination. This is more than just putting any old drugs together. Here are some treatment strategies from the world of HIV care.

### First time on therapy

"Treatment naïve" refers to people who've never taken HIV therapy before. Your first two drug regimens have the best chance to bring the level of HIV in your blood down to undetectable. These beginning combinations can be among the simplest. Combivir/Sustiva is probably the most popular. Now that there's Epzicom and Truvada on the market, they might take the place of the Combivir in that regimen.

Some doctors prefer starting people out on a protease inhibitor (PI), and Kaletra is the leader of the pack for these drugs. But Reyataz, which is taken only once a day, may soon challenge Kaletra's lead position. Reyataz also has the advantage of not raising lipid levels (cholesterol and triglycerides).

Some treatment naïve people might even be able to take Trizivir—one pill, twice a day. But because a recent study demonstrated that twice as many people failed Trizivir as other regimens that included a PI or NNRTI, few doctors today would start with Trizivir alone. Those people already on Trizivir who have undetectable viral loads, however, need not alter their therapy.

So know your options and try to pick a regimen that you can live with (such as number of pills and potential side effects).

### Treatment experienced, or salvage regimens

As more drugs and drug combinations are taken, you can expect less effectiveness—a viral load above the level of detectable. But that's not always so bad. Studies find lots of people doing well on stable, detectable viral loads (but not real high levels). Drug therapy is keeping people out of the hospital. Again, know your options.

### Boosting

Norvir, a PI once used to treat people with HIV, is now used to boost the drug levels of other PIs, making them more potent and durable, and allowing less pills. At the low levels prescribed for boosting, Norvir has far fewer side effects than it did in its original, six pill twice-a-day, formulation. The most powerful boosted PI today is Kaletra, which combines lopinavir with a tiny dose of Norvir.

### Combo drugs

Combination pills—those with two or more drugs in it—are cutting the number of pills people take. Current combo pills on the HIV market are: Combivir, Trizivir, Epzicom and Truvada. In the works is a new combo pill, one that—for the first time—contains two classes of HIV drugs. That's the combination of Sustiva and Truvada.

### Nuke backbone

Most HIV regimens contain two (sometimes more) nucleoside analogs. This is called the "nucleoside backbone" of the combination.

### Dual PI combos

Combining two PIs can be effective in suppressing HIV, sometimes without adding nukes or a non-nuke. The idea is to use two full-dose PIs together, rather than just boosting one PI with a small dose of Norvir. A powerful combination is Kaletra and saquinavir (Invirase or Fortovase). Studies are also looking at the combination of Kaletra and Reyataz. Kaletra and Agenerase or Lexiva should be combined with caution, because the latter two drugs lower the blood levels of the lopinavir component of Kaletra. Dual PI combos are generally salvage therapies, when a person can usually no longer take simpler regimens.

### Class-sparing regimens

There are four classes of HIV drugs on the market (five if you want to get technical—Viread is a nucleotide instead of a nucleoside analog). Treatment usually consists of meds from two or three of the classes. The idea behind class sparing is that you have a class of drugs you've never used before, in case you need it later on. It's also used to avoid the potential side effects and toxicity associated with a particular class of drugs.

Almost no one takes three classes of drugs for their first regimen, so they're automatically "class-sparing." The newest concept in class-sparing regimens is dual PIs (see above). Nuke-only therapy is to be avoided, although Trizivir with Viread has had early success and might prove to be an effective combination.

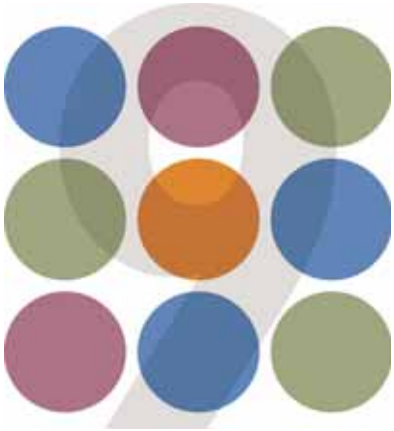
### Kaletra monotherapy

Among the most radical approaches to pop up over the past year or so, this concept shows promise because of Kaletra's high potency and durability, and lack of drug resistance in treatment-naïve people. But for now, don't try this at home. It's still in early, small studies.

### Induction/Maintenance

The idea behind induction/maintenance is to hit the virus "hard" early with four or five anti-HIV medications from multiple classes, then back off with fewer medications later. If a person could be maintained on two medications, for example, compliance might improve and there might be fewer side effects. With such an approach, however, there is the risk of failure—the virus might break through, becoming resistant to the lower-dose regimen.

*Special thanks to Ross Slotten, M.D., for reviewing this article.*



# The Ninth Annual HIV Drug Guide

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## Overview/Introduction

- Each drug must be taken in combination with at least one other drug (with the possible exception of Trizivir)
- Drugs are listed within their class in order of the date of their approval by the U.S. Food and Drug Administration (FDA), but in alphabetical order within their class on the drug chart
- "Average Wholesale Price" (AWP) is a pharmacy baseline standard, and does not necessarily represent what your pharmacy or insurer paid
- Manufacturer contact can be used to obtain information on the company's Patient Assistance Program (free supply of medicine) for that drug
- "ARV" stands for "antiretroviral"
- Drugs separated by slashes below are combination drugs

**Brand Name:** Retrovir

**Common Name:** zidovudine (ZDV), AZT

## One 300 mg tablet twice daily

**Class:** nucleoside analog (also called nucleoside reverse transcriptase inhibitor, NRTI or nuke)

**Standard dose:** One 300 mg tablet twice-a-day (two 100 mg capsules three times a day also available), no food restrictions (may be taken with or without food). Clear, strawberry-flavored liquid available for pediatric use. Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $387.38 / month

**Manufacturer contact:** GlaxoSmithKline, www.treathiv.com, 1 (800) 722–9294

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Most common side effects include headaches, fever, chills, muscle soreness, fatigue, nausea, and fingernail discoloration. AZT has been associated with alteration of various cells in the blood through bone marrow suppression resulting in anemia (low red blood cells) and/or neutropenia (low white blood counts), particularly in people with advanced HIV during the first three months. Potential for severe anemia requiring blood transfusion or hospitalization when used on its own or in combination with hydroxyurea. Prolonged use of high doses of AZT has been associated with symptomatic myopathy (muscle damage). Rare but potentially fatal toxicity with all NRTIs is pancreatitis (inflammation of the pancreas), hepatomegaly (enlarged liver) with steatosis and lactic acidosis (accumulation of lactate in the blood and abnormal acid-base balance). Lactic acidosis has been seen in patients taking NRTIs but is more common and more severe in women, people who are obese and people who have been taking nukes for a long time; and more common in people with liver disease, but can occur in people without a history of liver damage. People with lactic acidosis may experience persistent fatigue, abdominal pain or distension, nausea/vomiting, and difficulty breathing or shortness of breath; and enlarged, fatty liver (called hepatomegaly with steatosis).

Pancreatitis can be life-threatening and may cause pain in the stomach and back, along with nausea, vomiting and blood in the urine. Your physician will check for pancreatitis by checking for increased levels of amylase and lipase in the blood. Risks for pancreatitis include: higher than recommended doses of NRTIs, advanced HIV, and alcohol use. The risk for pancreatitis with AZT is low compared to didanosine.

**Potential drug interactions:** Biaxin, Dilantin, Mycobutin, and rifampin (under various brand names) may decrease AZT blood levels. Benemid and Depakote may increase AZT blood levels and decrease AZT clearance. Cytovene, Vitrasert and Valcyte increase AZT blood levels, and perhaps AZT-related anemia. Prescriber may need to adjust doses accordingly. AZT and Zerit should not be used together due to evidence that one limits the other's effectiveness. Also, bone marrow supression should be monitored with use of ganciclovir, amphotericin B, pentamidine, dapsone, flucytosine, sulfadiazine, interferon-alpha, ribavirin (Rebetol), and with other antineoplastics (anti-tumor treatment) such as hydroxyurea and doxorubicin. Ribavirin and AZT may cancel each other out and may increase the risk of lactic acidosis, therefore combination use should be avoided.

**Tips:** Outstanding news for AZT this year: it came to the rescue of triple nuke therapy. After the bad news that the two most potent nukes, Viread and Ziagen, failed badly in the triple-nuke combination with Epivir, came the good news that the three drugs worked well in the nuke-only regimen of Trizivir/Viread. AZT (found in Trizivir) helps fight off the drug resistance problems that plague triple nukes that don't include it. These results are still preliminary. A nuke-only regimen should only be tried by people with low viral loads (below 50,000)—see aidsinfo.nih.gov for a full discussion. The not-so-good news for people adding AZT: the fatigue and the potential anemia. You can start taking Procrit for some anemias, but that's adding an expensive weekly injectible. Some doctors would prefer switching out the AZT for another drug. Also, some clinicians are avoiding the "T" drugs, or thymidine analogs (AZT and Zerit) because of implication in lipoatrophy. Taking with food may minimize upset stomach. Studies show that AZT crosses the blood-brain barrier to a useful degree, which may be beneficial for patients at risk for neurological damage (such as dementia) from HIV. Proven to significantly reduce mother-to-infant transmission. Also available in Combivir (with Epivir) and in a triple combination in Trizivir (with both Epivir and Ziagen).

### Doctor

Retrovir was the first anti-HIV medication approved by the FDA for the treatment of HIV/AIDS and, eighteen years later, it is still a mainstay of therapy. Retrovir's most serious side effect is anemia, which occurs in less than five per cent of patients; it may also play a role in the lipodystrophy syndrome (see Zerit). In high doses, Retrovir penetrates the blood-brain barrier, making it useful for the treatment of some HIV-related neurological syndromes. It continues to be highly effective in preventing maternal-fetal transmission of HIV; and it is frequently part of a regimen to prevent the transmission of HIV in the workplace, especially through needle stick injuries. —Ross Slotten, MD

### Activist

As the first approved HIV drug, AZT has had the most time and opportunity to reveal itself to us. It has remained a reliable and effective component of many antiretroviral regimens used by lots of people, with great success. It has proven broad application—dementia, pregnancy, and post-exposure prophylaxis, for example. A fall from favor won't be because it lacks durability or effectiveness, but because of side effects and toxicities. Nausea, headaches, muscle pain and bone marrow suppression are all associated with it. Even though early days of testing (using doses that proved too high and very toxic—and useless without other agents to combine it with) resulted in a loss of community cred, there is no denying AZT's utility in fighting HIV, including ARV-resistant virus. After the patent expires this year, expect to see other companies put it with their drugs in combination pills. —Heidi M. Nass

## One 400 mg capsule once daily

**Class:** nucleoside analog (also called nucleoside reverse transcriptase inhibitor, NRTI or nuke)

**Standard dose:** One 400 mg enteric coated (Videx EC) delayed-release capsule once-a-day, with adjustments for weight and when combined with Viread or Truvada. (Also available in 125 mg, 200 and 250 mg caps.) For the older formulation of Videx, standard dose is two 100 mg buffered tablets twice-a-day (or four tablets once daily). Videx is also available as a buffered powder for oral solution. Take Videx and Videx EC strictly on an empty stomach, 30 minutes before or two hours after food or drink, except water. Take missed dose as soon as possible, but do not double up on the next dose. Generic Videx EC now available.

**AWP:** $328.22 / month for EC

**Manufacturer contact:** Bristol-Myers Squibb, www.bmsvirology.com, 1 (800) 272–4878

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Peripheral neuropathy (tingling, burning, numbness or pain in the hands or feet) may go away once didanosine is stopped, but can be painful and permanently debilitating if not treated in time and occurs more frequently when used with Zerit. Upset stomach (nausea and vomiting), diarrhea, headache, and more rarely pancreatitis (inflammation of the pancreas) has also been reported. Other toxicities include eye changes and optic neuritis (inflammation of nerves in the eye). Have periodic eye exam by someone who is aware you are HIV-positive. Increased uric acid levels (indicating a number of disorders, including kidney damage and metabolic diseases), and insomnia are other potential side effects. Rare but potentially fatal toxicity with all NRTIs is pancreatitis (inflammation of the pancreas), hepatomegaly with steatosis (enlarged, fatty liver) and lactic acidosis (accumulation of lactate in the blood and abnormal acid-base balance). Lactic acidosis has been seen in patients taking NRTIs but is more common and more severe in women, people who are obese and people who have been taking nukes for a long time; and more common in people with liver disease, but can occur in people without a history of liver damage. People with lactic acidosis may experience persistent fatigue, abdominal pain or distension, nausea/vomiting, and difficulty breathing or shortness of breath; and enlarged, fatty liver.

People with a history of peripheral neuropathy, pancreatitis or heavy alcohol use should avoid didanosine. Pancreatitis can be life-threatening and may cause pain in the stomach and back, along with nausea, vomiting and blood in the urine. Risks for pancreatitis include: higher than recommended doses of NRTIs, advanced HIV, and alcohol use. Body fat redistribution/accumulation has also been reported with didanosine.

**Potential drug interactions:** The levels of didanosine are increased by 44–60% when given at the same time as Viread (tenofovir), therefore a dose reduction to 250 mg for Videx is recommended. See Viread page for new, possibly worrisome, information. The dose of didanosine may need to be increased when taken with methadone. The combined use of didanosine and zalcitabine (Hivid) is not recommended because of the higher incidence of peripheral neuropathy. Antineoplastics (anti-tumor treatment) such as AZT and hydroxyurea may increase risk of peripheral neuropathy. Combining didanosine with stavudine (Zerit) or with hydroxyurea (Hydrea), alcohol, Cytovene, or NebuPent may increase risk of pancreatitis. Also, Cytovene substantually increases didanosine levels. Videx should be taken on an empty stomach two hours apart from protease inhibitors, Tagamet, Nizoral, Sporanox and dapsone, and one hour apart from Rescriptor, while Videx EC can be taken with them, but still on an empty stomach. With Viread, it may be taken with a light snack (low-fat, 373 calories).

**Tips:** Study indicates Videx EC (compared to Videx) may have lower risk of peripheral neuropathy. Either drug taken with Zerit increases the risk of lipoatrophy (facial wasting). Swallow the capsules whole (don't break open or bite/chew). The capsules eliminate the bad taste and texture of the tablets and the enteric coating reduces diarrhea. Absorption can be decreased by as much as 50% when taken with food, so always try to take on an empty stomach. Antacids containing magnesium or aluminum may cause adverse side effects if given at the same time as Videx tablets. If you have reduced kidney function, you may require a lower dose. Notify your doctor immediately if peripheral neuropathy is suspected.

### Doctor

Videx was the second NRTI approved by the FDA. Once an unpleasant chewable tablet, it has since been reformulated into a more palatable enteric-coated (EC) capsule given once daily, though with the same dietary restrictions as its precursor. Its primary side effects are pancreatitis and peripheral neuropathy, which occur more commonly in people with advanced HIV disease. Combining it with Zerit may increase the frequency of these adverse reactions. It has also been implicated as a cause of lipodystrophy. —Ross Slotten, MD

### Activist

I didn't live through AZT monotherapy or liquid Norvir, but I have a few battle scars from ddI. By the time the new formulation came out (a h-h-huge improvement over the old buffered versions), my pancreas and I were long gone. The potential side effect and toxicity profile—pancreatitis, neuropathy, diarrhea—isn't one that makes you say, "Sign me up!" However…and there's almost always a "however" in any treatment decision…if you're looking for a once daily drug that doesn't require food and you've been through other drugs in this class, you may want to look at ddI. The thing to navigate is its interactions with other drugs. You'll have to double-check your antacids, and more than a little alcohol won't do your liver any favors. We knew to avoid combining ddI and d4T, but it's recently clear that using ddI—even at a smaller dose—with tenofovir is asking for trouble, too. —Heidi M. Nass

**Brand Name:** Hivid

**Common Name:** zalcitabine, ddC

## One 0.75 mg tablet three times daily

**Class:** nucleoside analog (also called nucleoside reverse transcriptase inhibitor, NRTI, or nuke)

**Standard dose:** One 0.75 mg tablet three times a day, take on an empty stomach. Liquid available through compassionate use program. Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $273 / month

**Manufacturer contact:** Roche Pharmaceuticals, www.rocheusa.com, 1 (800) 282–7780

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Peripheral neuropathy (tingling, burning, numbness or pain in the hands or feet) may go away once Hivid is stopped, but can be painful and permanently debilitating if not treated in time. Other side effects include headache, fever, skin eruptions, sores or swelling in the mouth, nausea, and pancreatitis. Rare but potentially fatal toxicity with all NRTIs is pancreatitis (inflammation of the pancreas), hepatomegaly (enlarged liver) with steatosis and lactic acidosis (accumulation of lactate in the blood and abnormal acid-base balance). Lactic acidosis has been seen in patients taking NRTIs but is more common and more severe in women, people who are obese and people who have been taking nukes for a long time; and more common in people with liver disease, but can occur in people without a history of liver damage. People with lactic acidosis may experience persistent fatigue, abdominal pain or distension, nausea/vomiting, and difficulty breathing or shortness of breath; and enlarged, fatty liver (called hepatomegaly with steatosis).

People with a history of peripheral neuropathy, pancreatitis or heavy alcohol use should avoid Hivid. Pancreatitis can be life-threatening and may cause pain in the stomach and back, along with nausea, vomiting and blood in the urine. Your physician will check for pancreatitis by checking for increased levels of amylase and lipase in the blood. Risks for pancreatitis include: higher than recommended doses of NRTIs, advanced HIV, and alcohol use. Body fat redistribution/accumulation has also been reported with Hivid. With few exceptions, these side effects are stronger than is seen with other NRTIs.

**Potential drug interactions:** Due to increased risks associated with peripheral neuropathy, Hivid should not be taken with Videx (ddI) or Zerit (d4T). Epivir (3TC) should also be avoided as it can lower the levels of Hivid in the body. Other medications that can interact with Hivid include Antabuse (disulfiram), Fungizone (amphotericin B), Benemid (probenecid), Chloromycetin (chloramphenicol), certain chemotherapy agents, Dilantin (phenytoin), dapsone, Foscavir (foscarnet), isoniazid, Flagyl (metronidazole), hydralazine, ribavirin, and Macrodantin/Macrobid (nitrofurantoin). When used at the same time as Tagamet (cimetidine) and Benemid (probenecid) monitor for renal toxicity. Maalox and Foscavir may decrease Hivid levels. When used with Hivid, pentamidine (NebuPent, Pentam or Pentacarinat, used for treating Pneumocystis jiroveci pneumonia (PCP), may increase risk of pancreatitis. Hivid should not be taken at the same time with antacids containing magnesium or aluminum, as they may decrease levels of Hivid in the body.

**Tips:** For a long time rarely used, Hivid is being prescribed more in salvage therapy. Hivid should be avoided if you are pregnant or breast feeding. Notify your doctor immediately if peripheral neuropathy is suspected, but do not stop medication unless directed to do so by your healthcare provider.

### Doctor

Hivid is an NRTI no longer commonly used because of its three-times-daily dosing frequency. Its primary toxicity is peripheral neuropathy; it therefore cannot be combined with Zerit or Videx. However, it can be given with Retrovir. Hivid may have a role in salvage therapy, although the presence of multiple nucleoside analog mutations (NAMS) will limit its efficacy. —Ross Slotten, MD

### Activist

Want to meet someone who's actually been on ddC? Head for the person you know who's been living with HIV the longest. It doesn't really surface in treatment decision-making anymore. Its lack of potency and its obnoxious side effect/toxicity profile are a prohibitive one-two punch. To quote the federal treatment guidelines, ddC "is less convenient (given three times daily) and more toxic and should rarely if ever be used." Amen. —Heidi M. Nass

## One 40 mg capsule twice daily

**Class:** nucleoside analog (also called nucleoside reverse transcriptase inhibitor, NRTI, or nuke)

**Standard dose:** One 40 mg capsule twice-a-day for people weighing 132 pounds (60 kg) or more, or one 30 mg capsule twice-a-day for people weighing less; no food restrictions (may be taken with or without food). Zerit is also available in 15 mg, 20 mg, 30 mg and 40 mg capsules and a powder for oral solution; check for food restrictions. An approved extended-release (XR) formulation has yet to be manufactured. Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $366 / month for 40 mg

**Manufacturer contact:** Bristol-Myers Squibb, www.bmsvirology.com, 1 (800) 272–4878

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Peripheral neuropathy (tingling, burning, numbness or pain in the hands or feet) may go away once Zerit is stopped, but can be painful and permanently debilitating if not treated in time. Additive lipoatrophy (facial wasting) and mitochondrial toxicities when combined with Videx or Hivid. Caregivers of young children should be instructed regarding noticing and reporting peripheral neuropathy. Adverse reactions and serious laboratory abnormalities in children were similar in type and frequency to those seen in adults. Other side effects include headache, chills/fever, malaise (general ill feeling), insomnia, anxiety, depression, rash, upset stomach (nausea and vomiting), diarrhea and abdominal pain. Rare but potentially fatal toxicity with all NRTIs is pancreatitis (inflammation of the pancreas), hepatomegaly with steatosis (enlarged, fatty liver) and lactic acidosis (accumulation of lactate in the blood and abnormal acid-base balance). Lactic acidosis has been seen in patients taking NRTIs but is more common and more severe in women, people who are obese and people who have been taking nukes for a long time; and more common in people with liver disease, but can occur in people without a history of liver damage. People with lactic acidosis may experience persistent fatigue, abdominal pain or distension, nausea/vomiting, and difficulty breathing or shortness of breath; and enlarged, fatty liver. People with a history of peripheral neuropathy, pancreatitis or heavy alcohol use should avoid Zerit. Pancreatitis can be life-threatening and may cause pain in the stomach and back, along with nausea, vomiting and blood in the urine. Stop taking Zerit immediately if exeriencing symptoms of pancreatitis and seek immediate medical attention. Your physician will check for pancreatitis by checking for increased levels of amylase and lipase in the blood. Risks for pancreatitis include: higher than recommended doses of NRTIs, advanced HIV, and alcohol use. Lipodystophy ("buffalo hump"), fat loss (lipoatrophy) in the face and limbs (arms and legs), and central fat accumulation has been associated with Zerit. Zerit and AZT are the HIV drugs (the thymidine analogs) most implicated by studies as causing lipoatrophy. Zerit also seems to be implicated in blood lipid (fat) increases, particularly triglycerides.

**Potential drug interactions:** When used in combination with Zerit, drugs such as Fungizone (amphotericin B), Foscavir (foscarnet), dapsone, and some drugs used to treat HIV may increase the risk of developing peripheral neuropathy. Cytovene and Vitrasert (ganciclovir), valganciclovir (Valcyte), intravenous Pentam (pentamidine), and Videx (ddI) may increase the risk of pancreatitis. Should be used with caution by people with pre-existing bone marrow suppression, renal insufficiency or peripheral neuropathy. AZT and Zerit should not be used together due to evidence that one limits the other's effectiveness. Because of additive neurotoxicity, if possible, Zerit should not be combined with zalcitabine (Hivid) or ddI.

**Tips:** Late last year, Zerit was moved from the list of "preferred" drugs to "alternate" drugs, according to U.S. HIV treatment guildlines, "due to increasing reports of stavudine-associated toxicities." Contact your healthcare provider immediately if peripheral neuropathy is suspected, but do not stop taking medication unless directed to do so by your healthcare provider. Studies show that Zerit crosses the blood-brain barrier to a useful degree, which may be beneficial for patients at risk for neurological damage (such as dementia) from HIV. Many leading HIV advocates are adamant that Zerit is associated with facial wasting and should be avoided.

### Doctor

Zerit is given twice daily. A once-daily formulation has been approved by the FDA but not released by its manufacturer. Like Videx, its most serious side effects are peripheral neuropathy and pancreatitis. Zerit has been implicated as one of the major causes of lipodystrophy, characterized by loss of facial fat, thinning of the arms and legs due to fat loss, and accumulation of fat on the back of the neck and abdomen. The exact mechanism of this syndrome, however, has not been fully worked out. Stopping Zerit (or any other drug contributing to lipodystrophy) will not reverse the abnormal distribution of fat, but may stop it from progressing. —Ross Slotten, MD

### Activist

My first antiretroviral regimen in 1998 included d4T and ddI—a combination that would be avoided today because of the compounded risk of neuropathy and pancreatitis when the two are used together. In fact, the federal treatment guidelines no longer recommend d4T as a "preferred" drug for people taking their first antiretroviral regimen. It has been implicated for some time—early and loudly in the community—in the development of lipoatrophy (and underlying mitochondrial damage inside cells), and clinical trials eventually verified both. Studies show it's as effective as other NRTIs, but the price tag is higher—more lipoatrophy, more neuropathy, and greater lipid increases. If you have to take d4T, keep a close eye on your lab values (liver, pancreas) and the mirror—if you notice changes, especially in your face, do…not…ignore…them. Heading off facial wasting and neuropathy is better than any treatments you'll find for them, at least for now. —Heidi M. Nass

**Brand Name:** Epivir

**Common Name:** lamivudine, 3TC

## One 300 mg tablet once daily

**Class:** nucleoside analog (also called nucleoside reverse transcriptase inhibitor, NRTI, or nuke)

**Standard dose:** One 300 mg tablet once-a-day (or one 150 mg tablet twice daily), with no food restrictions (may be taken with or without food). Dose is lower for people with kidney impairment and in children and people who weigh less than 110 pounds (50 kg), to 2 mg/kg (a kilogram equals 2.2 pounds). A strawberry/banana flavored liquid is also available. Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $331.53 / month for 300 mg

**Manufacturer contact:** GlaxoSmithKline, www.treathiv.com, 1 (800) 722–9294

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** This remains one of the most easily tolerated HIV medications. Potential side effects/toxicities include headache, nausea, diarrhea, fatigue, hair loss, insomnia, malaise (general ill feeling), nasal symptoms, cough, peripheral neuropathy, low white blood cells and anemia.

Rare but potentially fatal toxicity with all NRTIs is pancreatitis (inflammation of the pancreas), hepatomegaly with steatosis (enlarged, fatty liver) and lactic acidosis (accumulation of lactate in the blood and abnormal acid-base balance). Lactic acidosis has been seen in patients taking NRTIs but is more common and more severe in women, people who are obese and people who have been taking nukes for a long time; and more common in people with liver disease, but can occur in people without a history of liver damage. People with lactic acidosis may experience persistent fatigue, abdominal pain or distension, nausea/vomiting, and difficulty breathing or shortness of breath; and enlarged, fatty liver. Pancreatitis can be life-threatening and may cause pain in the stomach and back, along with nausea, vomiting and blood in the urine. Your physician will check for pancreatitis by checking for increased levels of amylase and lipase in the blood. Risks for pancreatitis include: higher than recommended doses of NRTIs, advanced HIV, and alcohol use. Children should be monitored carefully for pancreatitis.

**Potential drug interactions:** No significant drug interactions.

**Tips:** Exciting news: drug resistance that the virus develops against Epivir—the M184V mutation—makes the virus less fit to replicate and has even been shown to keep T-cells from dropping as much as they would have otherwise. It is also approved for treatment of hepatitis B virus (HBV), under the brand name Epivir HBV. So if you have hepatitis B and HIV, this drug works for both diseases, but make sure you are taking Epivir at HIV doses—always ask your doctor or pharmacist. Worsening of hepatitis B (HBV) in people co-infected with HIV/HBV has occurred when Epivir was discontinued. Epivir is also available combined with Retrovir (Combivir, one tablet twice-a-day), in a new once-a-day formula with Ziagen (Epzicom, one tablet daily) and in a triple combination with both Retrovir and Ziagen (Trizivir, one tablet twice-a-day).

### Doctor

Epivir is a potent NRTI usually used in combination with Retrovir, Zerit, Videx, Ziagen or Viread to form the so-called nucleoside backbone of anti-retroviral therapy. Its low toxicity and ease of administration (it can now be dosed once daily) make it an ideal medication for the treatment of HIV/AIDS; but its hallmark resistance mutation, M184, occurs rapidly if a patient is not compliant with his or her regimen. Viruses with the M184 mutation are considered "less fit" than the natural, nonresistant, form of the virus, which means that disease progression is slower if the person continues on Epivir even when resistant to it. —Ross Slotten, MD

### Activist

In the pageant of ARVs, 3TC would win "Most Popular". It was the fifth, and friendliest, ARV approved. Potent, easy to take, minimal side effects—it has lovely features, you might say. The only thing to harsh on your mellow is that resistance to 3TC develops really easily. However, 3TC-resistant virus has less punch and this resistance can make HIV more susceptible to other ARV drugs. No wonder, then, it turns up in countless first-line regimens and is often kept on board even after resistance to it develops. You'll also find a daily dose of it in Trizivir, Combivir and Epzicom. For people with HIV and hepatitis B, 3TC is a twofer—it is approved for HBV treatment, though it should be taken at the HIV dose if you have both viruses, and care must be taken if it is stopped suddenly because HBV can rebound and damage the liver. —Heidi M. Nass

## Two 300 mg tablets once daily

**Class:** nucleoside analog (also called nucleoside reverse transcriptase inhibitor, NRTI, or nuke)

**Standard dose:** Two 300 mg tablets once-a-day (or one 300 mg tablet twice-a-day), no food restrictions (may be taken with or without food). A strawberry/banana flavored liquid is available. Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $445.50 / month

**Manufacturer contact:** GlaxoSmithKline, www.ziagen.com, 1 (800) 722–9294

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Hypersensitivity reaction (HSR, an allergic-like reaction). Approximately 5% of people (1 in 20) taking abacavir experienced HSR during clinical trials. People who think they are experiencing HSR must be evaluated by an experienced HIV provider as soon as possible before they stop taking abacavir. Be very careful, especially in the first two months of treatment. Symptoms worsen with every dose, but very slowly. If treatment is stopped by the medical provider because of this serious reaction, they can never take abacavir, Epzicom or Trizivir again (called "rechallenging") because of life-threatening and potentially fatal reaction. (This does not apply to missed doses, when there's no HSR, but watch for symptoms if you've stopped the drug for at least a few days). This reaction usually occurs during the second week of treatment, but may take as long as six weeks to appear, gets progressively worse and resolves quickly (24–48 hours) after permanent discontinuation. Symptoms usually, but not always, include some combination of sudden fever, muscle ache, severe nausea, vomiting or abdominal pain, severe tiredness, respiratory symptoms (cough, difficulty breathing and sore throat) and possibly mild rash. These symptoms are listed on the patient information sheet and warning card that you receive each time you fill your Ziagen prescription. You should always keep the warning card with you. HSR might be confused with flu during flu season, but remember that it worsens with every dose. See Epzicom tips.

More common side effects include nausea, vomiting, diarrhea, fatigue, headache, fever, rash, anorexia (loss of appetite), and potentially high blood sugar and high triglyceride levels (fat in the blood). Rare but potentially fatal toxicity with all NRTIs is pancreatitis (inflammation of the pancreas), hepatomegaly (enlarged liver) with steatosis and lactic acidosis (accumulation of lactate in the blood and abnormal acid-base balance). Lactic acidosis has been seen in patients taking NRTIs but is more severe in women, especially those overweight; and more common in people with liver disease, but can occur in people without a history of liver damage. Symptoms include persistent fatigue, abdominal pain or distension, nausea/vomiting, and difficulty breathing or shortness of breath; and enlarged, fatty liver (called hepatomegaly with steatosis). Pancreatitis can be life-threatening and may cause pain in the stomach and back, along with nausea, vomiting and blood in the urine. Check for pancreatitis by checking for increased levels of amylase and lipase in the blood. Risks for pancreatitis include: higher than recommended doses of NRTIs, advanced HIV, and alcohol use. Children should be monitored carefully for pancreatitis.

**Potential drug interactions:** Excessive alcohol increases abacavir levels and might increase its side effects. People with moderate to severe cirrhosis should use abacavir with caution. No clinically significant interactions between abacavir and other drugs have been observed.

**Tips:** Studies show that abacavir crosses the blood-brain barrier to a useful degree, which may be beneficial for patients at risk for neurological damage (such as dementia) from HIV. The pattern of viral resistance to abacavir is similar to that of other NRTIs, though abacavir can retain some activity when other NRTI's have lost most activity.

The manufacturer recommends that people with symptoms of acute respiratory disease consider hypersensitivity even if other diagnosis such as pneumonia, bronchitis or flu is possible, but this is undoubtedly a legal issue. Be careful before you unnecessarily drop Ziagen, and burn through a potent and tolerable HIV drug. Check with your doctor if you have any side effects after taking this medicine—*don't just stop!* Doctors report seeing a higher incidence of HSR in people taking abacavir as part of their first drug regimen (Studies done comparing side effects were with this group.). An analysis of 8,000 patients found a reduced risk of HSR in blacks and in men.

### Doctor

Ziagen is one of the newer NRTIs and can now be dosed once daily. Its barrier to resistance is higher than many of the other NRTIs, meaning that multiple nucleoside resistance mutations are required to make it ineffective. Its main potential adverse effect is a hypersensitivity reaction, characterized by nausea and vomiting shortly after taking a dose, usually occuring 7 to 14 days after starting. When the medication is stopped, the reaction resolves quickly; but it should never be given again because the next reaction could be fatal. Fortunately, hypersensitivity to Ziagen is rare—approximately five per cent of the population may have a genetic tendency to develop it, though no test exists for screening. Unfortunately, the dangers of this potent, otherwise well-tolerated drug have been greatly exaggerated, inhibiting its use as a first-line agent. —Ross Slotten, MD

### Activist

Approximately 5-7% of people who take abacavir get a very serious hypersensitivity reaction, which is resolved by stopping the drug and never restarting it. I think abacavir has been held hostage by the very idea that this reaction can occur—it freaks out people thinking of using it and clinicians get nervous about using it in various situations. The worst-case scenario: the drug is stopped without a provider laying eyes on the symptoms. No diagnosis is made and hypersensitivity must be presumed. In that scenario a good drug (and one that does less mitochondrial damage…so less lipoatrophy?…than some others in its class) is gone for good. If you get "flu-like symptoms" in the weeks after you start, call your clinic right away. The perfect scenario: they'll have you come in and take your next dose so they can see if the symptoms worsen after dosing. —Heidi M. Nass

**Brand Name:** Ziagen

**Common Name:** abacavir sulfate (ABC)

## Brand Name: Combivir

### One tablet twice daily

**Class:** nucleoside analog (also called nucleoside reverse transcriptase inhibitor, NRTI or nuke)

**Standard dose:** One tablet (150 mg lamivudine, 3TC, Epivir, 300 mg zidovudine, AZT, Retrovir), twice-a-day, with no food restrictions (may be taken with or without food). Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $718.85 / month

**Manufacturer contact:** GlaxoSmithKline, www.combivir.com, 1 (800) 722–9294

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** May be taken with food to decrease potential nausea associated with AZT. See drug pages for lamivudine, 3TC (Epivir) and zidovudine, AZT (Retrovir) for more details.

**Potential drug interactions:** See lamivudine, 3TC (Epivir) and zidovudine, AZT (Retrovir). Do not take Retrovir or Epivir while taking Combivir since these medications are already in Combivir.

**Tips:** Combivir has proven to be the best dual-nucleoside backbone studied and is the preferred nucleoside combination to take in both U.S. HIV treatment guidelines as well as those of the International AIDS Society-USA. It is the combination of lamivudine, 3TC (Epivir) and zidovudine, AZT (Retrovir) into one pill; see the pages of those individual drugs for more information. The AZT in Combivir can cause fatigue and anemia—it ain't pretty in those at risk for developing anemias (see Retrovir). But Combivir is still the most proven dual-nuke combo and every doctor out there should be comfortable with managing its side effects. Combivir brings with it one of the "T" drugs, or thymidine analogs (AZT and Zerit)—some clinicians are avoiding those when possible because of implication in lipoatrophy. If you are on it though, don't worry—Combivir is still an effective combination.

### Doctor

Combivir is the combined formulation of Retrovir and Epivir. —Ross Slotten, MD

### Activist

Old friends AZT and 3TC were put together in one pill by their manufacturer. It has the same effectiveness and side effect profile as the two drugs taken separately, but one less prescription co-pay! Of course, a sure sign of a sick health care system is treatment decisions based on cost instead of science. Bottom line, if AZT and 3TC are a good choice for you (and a well-studied combination it is)—congratulations! You've got yourself two less pills to swallow. —Heidi M. Nass

## One tablet twice daily

**Class:** nucleoside analog (also called nucleoside reverse transcriptase inhibitor, NRTI or nuke)

**Standard dose:** One tablet (300 mg abacavir, Ziagen, 150 mg lamivudine, 3TC, Epivir and 300 mg zidovudine, AZT, Retrovir), twice-a-day, no food restrictions (may be taken with or without food). Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $1,164.35 / month

**Manufacturer contact:** GlaxoSmithKline, www.treathiv.com, 1 (800) 722–9294

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** The most common side effects of Trizivir are the same as Epivir; Retrovir; and Ziagen. See those pages for more information. Side effects associated with Trizivir include headache, nausea, upset stomach, and fatigue. May be taken with food to decrease potential nausea associated with AZT. The hypersensitivity reaction (HSR, an allergic-like reaction) warning on abacavir (Ziagen) bears repeating here. Approximately 5% of people (1 in 20) taking abacavir experienced hypersensitivity during clinical trials. People who think they are experiencing hypersensitivity must be evaluated by an experienced HIV provider as soon as possible before they stop taking abacavir. If treatment is stopped because of this serious reaction, they can never take abacavir or Trizivir or Epzicom again (called "re-challenging") because of life-threatening and in a few instances fatal reaction. (This does not apply to missed doses, when there's no HSR.) This hypersensitivity usually occurs during the second week of treatment, but may take as long as six weeks to appear, gets progressively worse and resolves quickly (24–48 hours) after permanent discontinuation. Symptoms usually, but not always, include some combination of sudden fever, muscle ache, severe nausea, vomiting or abdominal pain, severe tiredness, respiratory symptoms (cough, difficulty breathing and sore throat) and possibly mild rash. These symptoms are listed on the patient information sheet and warning card that you receive each time you fill your prescription. You should always keep the warning card with you. Hypersensitivity might be confused with flu during flu season, but remember that HSR worsens with every dose. See Epzicom tips. Check with your doctor if you have any side effects after taking this medicine—*don't just stop!*

**Potential drug interactions:** See also Epivir, Retrovir and Ziagen for more information. Do not take Retrovir, Epivir or Ziagen while taking Trizivir since these medications are already in Trizivir. If you are taking one of the following medications, consult your doctor or pharmacist before starting Trizivir: stavudine, zalcitabine, ribavirin, interferon, rifabutin, rifampin, probenecid, methadone, ganciclovir, clarithromycin, pyramethamine, flucytosine, amphotericin B and hydroxyurea.

**Tips:** Good news for Trizivir last year: when combined with Viread, it was the sole successful nuke-only combination seen so far (see AZT page for more information). A study found that at 48 weeks (a significant amount of time), results were the same as in people taking the well-documented successful combination of Sustiva/Combivir. 39/40 people on Trizivir/Viread had less than 50 viral load at 48 weeks, compared to 40/40 people on Sustiva/Combivir. Taking into account all the people who actually started on therapy (before dropping out or moving away or whatever), the results were still an excellent 70% below 50 viral load. More importantly, only one person experienced virologic failure (not staying below undetectable viral load) on Trizivir/Viread. Both groups also had similar T-cell increases of 165 on Trizivir/Viread vs. 120 for Sustiva/Combivir. The participants were taking HIV medications for the first time, so they can be expected to do better. Still, the study shows that this nucleoside-only drug combination can be taken. The number of people is small, but then, they also started out with high viral load—more than 100,000. That's impressive. The drug resistance pattern of the AZT in Trizivir is what was found to save the day for nuke-only combination containing the potent Ziagen and Viread. Still, a nuke-only regimen should only be tried by people with low viral loads (below 50,000)—see aidsinfo.nih.gov for a full discussion.

### Doctor

Trizivir is the triple combination of Retrovir, Epivir and Ziagen. Initially marketed as equivalent to regimens containing a protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) to treat HIV, subsequent studies have raised questions about its potency. Eighty percent of patients on Trizivir in one study attained a durable response (that is, remain undetectable after 48 weeks) as compared to ninety per cent on other combination regimens—against a PI or NN. Its main appeal, however, is its simplicity and low rate of serious adverse effects, suggesting that adherence might be less of a problem in the long run. However, until long-term studies are completed, Trizivir should be combined with a drug in another class. —Ross Slotten, MD

### Activist

A few years back we were hopeful that Trizivir—AZT, 3TC and abacavir all in one pill—could be a durable, easy regimen. One pill twice daily with or without food—it sounded too good to be true, and it was. Just not potent enough, Trizivir didn't maintain viral suppression for people who'd never taken ARVs before, even those with lower viral loads starting out. These three nukes used alone are an invitation for broad resistance within an important class of ARVs. However, if your viral load is low and you've never taken HIV meds and you hate taking pills and you can't do a med that requires food and drug co-pays are killers for you…well, never say never. People on a regimen that includes these three agents get all the same effectiveness and side effects, but in a few less pills, which is no small thing. —Heidi M. Nass

**Brand Name:** Emtriva

**Common Name:** emtricitabine, FTC

## One capsule once daily

**Class:** nucleoside analog (also called nucleoside reverse transcriptase inhibitor, NRTI or nuke)

**Standard dose:** One 200 mg capsule once-a-day, with no food restrictions (may be taken with or without food). The dosing frequency needs to be adjusted for people who have decreased kidney function. Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $308.45 / month

**Manufacturer contact:** Gilead Sciences, www.gilead.com, 1 (800) GILEAD5 (445–3235)

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Most common side effects include headache, diarrhea, nausea and rash. Skin discoloration observed as a darkening of the skin on the palms and the soles of the feet can occur and usually does not cause any symptoms. Rare but potentially fatal toxicity with all NRTIs is pancreatitis (inflammation of the pancreas), hepatomegaly with steatosis (enlarged, fatty liver) and lactic acidosis (accumulation of lactate in the blood and abnormal acid-base balance). Lactic acidosis has been seen in patients taking NRTIs but is more common and more severe in women, people who are obese and people who have been taking nukes for a long time; and more common in people with liver disease, but can occur in people without a history of liver damage. People with lactic acidosis may experience persistent fatigue, abdominal pain or distension, nausea/vomiting, and difficulty breathing or shortness of breath; and enlarged, fatty liver. Pancreatitis can be life-threatening and may cause pain in the stomach and back, along with nausea, vomiting and blood in the urine. Your physician will check for pancreatitis by checking for increased levels of amylase and lipase in the blood. Risks for pancreatitis include: higher than recommended doses of NRTIs, advanced HIV, and alcohol use. Children should be monitored carefully for pancreatitis.

**Potential drug interactions:** No significant drug interactions observed in clinical trials.

**Tips:** Emtriva (FTC) is called a "me-too" drug because of its similarity to Epivir (3TC); both drugs are associated with the M184V mutation (which suggests drug resistance). However, Emtriva remains in blood cells in excess of the 24-hour dosing interval. It also remains inside of the cell longer with a steady state intracellular mean half-life of the active drug of 39 hours.

Due to cross-resistance, Epivir (3TC) and Emtriva (FTC) can lower the levels of Hivid, and should be avoided. Emtriva has demonstrated efficacy against HBV but is not currently approved to treat HBV. Worsening of hepatitis B (HBV) in people co-infected with HIV/HBV has occurred when Emtriva was discontinued. Patients co-infected with HIV/HBV who stop taking Emtriva should be closely followed by their physician. Available in a co-formulation with Viread, Truvada.

### Doctor

Emtriva is an NRTI that is nearly identical to Epivir. —Ross Slotten, MD

### Activist

If 3TC were a car and turned up on "Pimp my Ride", it would be unveiled by Xhibit at the end of the show as FTC—newly tricked out, for sure, but the same under the hood. FTC has the same resistance profile as 3TC, so it doesn't offer us anything there. In fact, the federal treatment guidelines really treat the two drugs as interchangeable—where lamivudine appears, "…or emtricitabine" follows. However, while 3TC eventually became a once daily drug, FTC came out of the gate as one. It has a longer half-life and more potency, at least in the short-term. Hopefully, this will translate into slower development of resistance. Time will tell whether it will be as well tolerated. Like 3TC, FTC is active against hepatitis B and stopping the drug can cause the HBV to flare. —Heidi M. Nass

## One tablet once daily

**Class:** nucleotide analog (also called nucleotide reverse transcriptase inhibitor—part of the nucleosides—NRTI, or nuke)

**Standard dose:** One 300 mg tablet once-a-day, with no food restrictions (with or without food). Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $485.56 / month

**Manufacturer contact:** Gilead Sciences, Inc., www.viread.com, 1 (800) GILEAD5 (445–3235)

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Overall, fairly well tolerated, however, individuals may experience the following: nausea, headache, diarrhea, vomiting, asthenia, flatulence, abdominal distension/pain and anorexia. See AZT page for rare but potentially fatal toxicity with all NRTIs as a drug class (they have not been seen with Viread).

The effect of tenofovir on children and individuals with severe hepatic (liver) impairment was not studied during drug development. However, since tenofovir is not metabolized by the liver (and appears to have less toxicity in the liver than the majority of the NRTIs), it is believed the impact on individuals with liver disease should be minimal.

**Potential drug interactions:** The levels of Videx EC and Videx (ddI) are increased by 44–60% when given at the same time as Viread. Therefore, a dose reduction to 250 mg for Videx is recommended. See tips. Viread decreases the concentration levels of Reyataz. In addition, Reyataz (and Kaletra) increases Viread concentrations. The reasons for these interactions are not fully understood. Higher Viread concentrations could increase the risk of Viread-associated adverse events, including renal disorders. The FDA suggests that patients receiving Reyataz and Viread should be monitored for Viread-associated adverse events. When taken with Viread, it is recommended that Reyataz 300 mg is given with Norvir 100 mg and Viread 300 mg (all as a single daily dose with food). Reyataz without Norvir should not be taken with Viread.

**Tips:** To its credit, Viread is successful in showing viral load decrease in people with nuke resistance. In three years of follow up studies, it continued to demonstrate good results in people whose current triple-class therapy is failing. The body clears 70–80% of Viread through the kidney and dosing adjustment is recommended for those with impaired kidney function. Serious kidney problems have been rare and the majority has been in those with pre-existing kidney disease or receiving nephrotoxic agents. However, the characteristics of renal toxicity are still being defined. More research is needed. The manufacturer recommends that individuals with impaired kidney function be monitored closely, especially in people with advanced HIV disease, even in people who did not start out with kidney disease. There have been about 20 reports on individuals who experienced severe kidney disorder including some taking Kaletra with Viread. Since Kaletra increases blood levels of Viread, it may increase the likelihood of Viread side effects. See Trizivir and AZT pages for successful results combining Viread with Trizivir. The drug resistance pattern of AZT in Trizivir was found to save the day for the nuke-only combination containing the potent Ziagen and Viread.

Recent bad news in combination with Videx—barely raising T-cells in people who are undetectable, failure to reach undetectable in people who started with less than 200 T-cells and more than 100,000 viral load—was met with nonchalance by many doctors, whose patients do well when taking the two drugs together. BMS sent a warning letter to doctors late last year reporting early virologic failure (detectable viral load) in a tiny number of people on HIV meds for the first time who were taking the combo with either Sustiva or Viramune. However, the letter points out that these individuals started out with a high viral load (not defined, but usually refers to more than 100,000) and that Viread and Videx-EC does well with protease inhibitors. But a larger study also found early failure (at 12 weeks) with Sustiva/Videx/Viread (12%, five out of 41 individuals) vs. Sustiva/Videx/Epivir (no failures at 12 weeks).

Like Epivir, Viread has activity against hepatitis B. Hepatitis B may flare up when Viread is discontinued. While data is limited, it appears that Viread can have prolonged activity against hepatitis B even when resistant to Epivir. Viread selects for the K65R mutation, (as does Ziagen and Videx), it was seen in 3% of the Viread treatment-naive patients at two years. But Viread continues to be effective despite this resistance. AZT and Zerit maintain full activity and varying rates of continued efficacy are seen with Ziagen and Videx. In clinical trials reduced response to Viread was associated with multiple TAMs (thymidine analog mutations), specifically the M41L or L210W. Further research needs to be done in this area.

### Doctor

Viread is a nucleotide analog, though it is classed with the nucleoside reverse transcriptase inhibitors. Like Epivir and Emtriva, it is well tolerated, though rarely it can impair kidney function, which returns to normal when the medication is stopped. Viread can interact with other anti-HIV medications, especially Videx and Reyataz. Other interactions may emerge in future studies. —Ross Slotten, MD

### Activist

After tenofovir was approved, the FDA got after Gilead a few times for overstating the drug's safety profile and potency in its promotions. (My rule: if there ever is a "miracle drug," as Gilead described Viread, we won't just hear about it in the company's ads.) Turns out, tenofovir is a fussy drug. It's potent and durable, but it doesn't play well with other once daily options: ddI, abacavir, atazanavir.... Tenofovir is cleared by the kidney (and will compete with other drugs cleared by the kidney, including some commonly used antivirals), so kidney function should be monitored closely. Despite an unfolding story of drug interaction (next up: Kaletra), tenofovir keeps showing its potential: possible maintenance therapy with efavirenz? Added to Trizivir as a second-line therapy? It's a drug on the move. Note: if you have HBV, the warning about stopping 3TC and FTC and risk of hepatic flare holds for tenofovir, too. —Heidi M. Nass

## One tablet once daily

**Class:** nucleoside analog (also called nucleoside reverse transcriptase inhibitor, NRTI or nuke)

**Standard dose:** One tablet (600 mg Ziagen/abacavir sulfate and 300 mg Epivir /3TC/ lamivudine), once a day, no food restrictions (may be taken with or without food). Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $758.38 / month

**Manufacturer contact:** GlaxoSmithKline, www.treathiv.com, 1 (800) 722–9294

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** The most common side effects of Epzicom are the same as Epivir and Ziagen. See those pages for more information.

**Potential drug interactions:** See also Epivir and Ziagen for more information. Do not take Epivir or Ziagen while taking Epzicom since these medications are already in Epzicom. The hypersensitivity reaction (HSR, an allergic-like reaction) warning on abacavir (Ziagen) bears repeating here. Approximately 5% of people (1 in 20) taking abacavir experienced hypersensitivity during clinical trials. People who think they are experiencing hypersensitivity must be evaluated by an experienced HIV provider as soon as possible before they stop taking abacavir. If treatment is stopped because of this serious reaction, they can never take abacavir or Trizivir or Epzicom again (called "re-challenging") because of life-threatening and in a few instances fatal reaction. (This does not apply to missed doses, when there's no HSR.) This hypersensitivity usually occurs during the second week of treatment, but may take as long as six weeks to appear, gets progressively worse and resolves quickly (24–48 hours) after permanent discontinuation. Symptoms usually, but not always, include some combination of sudden fever, muscle ache, severe nausea, vomiting or abdominal pain, severe tiredness, respiratory symptoms (cough, difficulty breathing and sore throat) and possibly mild rash. These symptoms are listed on the patient information sheet and warning card that you receive each time you fill your prescription. You should always keep the warning card with you. Hypersensitivity might be confused with flu during flu season, but remember that HSR worsens with every dose. See tips.

**Tips:** Remember, Epzicom is two drugs in one pill, so see the pages for those drugs, Epivir and Ziagen. Ziagen by itself is FDA approved for either once-a-day or twice-a-day dosing. The once-daily formula in Epzicom was found to have the same amount in the blood over 24 hours (bioequivalency) as Ziagen twice-a-day. The race is on: Epzicom, or Truvada? Both are a combination of two drugs taken as one pill, once a day. (This is called FDC, for "fixed-dose combination.") Both were approved by the FDA on the same day last August. All four drugs have already been out in the drug store. Moreover, two of the four drugs (Epivir and Emtriva) are virtually identical (except that Emtriva lasts longer in the blood; however, in head-to-head data, Emtriva did not do as well as Epivir 150 mg twice a day). Perhaps the quick and dirty way to divide the two is by toxicity: the drugs in Truvada are fairly tolerable (see Emtriva and Viread), however, more and more patients are complaining of abdominal distension due to excessive gas production and bloating. The Ziagen in Epzicom unfortunately has a hypersensitivity reaction (HSR) in anywhere from 5–8% of people taking it. The incidence of HSR was the same between Epzicom and Ziagen twice-a-day (8% vs. 9%), but the incidence of severe reactions was higher with Epzicom (5% vs. 2%). Remember that the HSR cited may have been suspected, not definitely diagnosed. Doctors say they see more HSR in people who are taking HIV meds for the first time. (Studies done comparing side effects were with this group.) Check with your doctor if you have any side effects after taking this medicine—don't just stop!

On the other hand, the toxicity and drug interactions with the Viread in Truvada are still being worked out. (See Viread for some of the problems that have arisen.)

Then there's resistance. K65R is the primary mutation for both Viread and Ziagen, so, you probably can't go from Epzicom to Truvada and expect to see huge improvement if your virus has come back while on Epzicom. And what about Truvada's longer lasting blood levels? Some doctors think that makes it a better choice, other doctors think otherwise, as that has yet to be determined. Many medical providers will say that the effect of half-life and of many of the resistance mutations—including K65R—have not been clinically proven. In other words, what does it do for your health? Experienced doctors, however, will avoid prescribing either FDC for people with the mutations at codon 103 on their resistance test.

How about Combivir vs. Epzicom? Glaxo has compared Combivir to Epzicom in a 48-week study, with comparable side effects.

### Doctor

Epzicom is the combined formulation of Epivir and Ziagen. Its primary advantage is its once-daily dosing. —Ross Slotten, MD

### Activist

The latest permutation of GSK drugs together in one pill, this combination of 3TC and abacavir is the debut of abacavir in a once-daily formulation. We should expect Epzicom to have all the same characteristics that the two drugs taken in separate pills would have, except that the hypersensitivity reaction may be more severe—though not more common—in people taking abacavir once daily than in people who take it twice daily. Once daily 3TC/abacavir is likeliest to be of more benefit to people who've never taken ARVs before than those who've been around the block with these drugs. —Heidi M. Nass

## One tablet once daily

**Class:** nucleoside/nucleotide analog (also called nucleoside or nucleotide reverse transcriptase inhibitor, NRTI or nuke)

**Standard dose:** One tablet (300 mg Viread/tenofovir disoproxil fumarate and 300 mg Emtriva/FTC/emtricitabine) once a day, no food restrictions (may be taken with or without food). Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $794 / month

**Manufacturer contact:** Gilead Sciences, www.gilead.com, 1 (800) GILEAD5 (445–3235)

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Overall, fairly well tolerated, however, individuals may experience the following: nausea, headache, diarrhea, rash, vomiting, asthenia, flatulence, abdominal distension/pain and anorexia. See AZT page for rare but potentially fatal toxicity with all NRTIs as a drug class (they have not been seen with Viread).

**Potential drug interactions:** The levels of Videx EC and Videx (ddI) are increased by 44–60% when given at the same time as Viread. Therefore, a dose reduction to 250 mg for Videx is recommended. See tips. Viread decreases the concentration levels of Reyataz. In addition, Reyataz (and Kaletra) increases Viread concentrations. The reasons for these interactions are not fully understood. Higher Viread concentrations could increase the risk of Viread-associated adverse events, including renal disorders. The FDA suggests that patients receiving Reyataz and Viread should be monitored for Viread-associated adverse events. When taken with Viread, it is recommended that Reyataz 300 mg is given with Norvir 100 mg and Viread 300 mg (all as a single daily dose with food). Reyataz without Norvir should not be taken with Viread.

**Tips:** Remember, Truvada is two drugs in one pill, so see the pages for those drugs, Emtriva and Viread. The race is on: Epzicom, or Truvada? Both are a combination of two drugs taken as one pill, once a day. (This is called FDC, for "fixed-dose combination.") Both were approved by the FDA on the same day last August. All four drugs have already been out in the drug store. Moreover, two of the four drugs (Epivir and Emtriva) are virtually identical (except that Emtriva lasts longer in the blood; however, in head-to-head data, Emtriva did not do as well as Epivir 150 mg twice a day). Perhaps the quick and dirty way to divide the two is by toxicity: the drugs in Truvada are fairly tolerable, however, more and more patients are complaining of abdominal distension due to excessive gas production and bloating. The Ziagen in Epzicom unfortunately has a hypersensitivity reaction (HSR) in anywhere from 5–8% of people taking it.

On the other hand, while kidney toxicity with the Viread in Truvada appears to be rare, the toxicity profile is still being worked out with this newer drug, and so are its drug interactions. (See Viread for some of the problems that have arisen.) Which brings up another difference—Epivir and Ziagen have been extensively studied, Emtriva and Viread have not. As a result, surprises continued to pop up with Viread after it hit the drug store.

Then there's resistance. Viread has a primary resistance mutation (K65R on a resistance test), but it's rare and Viread tends to continue to work for people even when they develop the mutation. K65R is also the primary mutation for Ziagen, so again, you probably can't go from Epzicom to Truvada and expect to see huge improvement if your virus has come back while on Epzicom.

And what about Truvada's longer lasting blood levels? Some doctors think that makes it a better choice, other doctors think otherwise, as that has yet to be determined. Many medical providers will say that the effect of half-life and of many of the resistance mutations—including K65R—have not been clinically proven. In other words, what does it do for your health? Experienced doctors, however, will avoid prescribing either FDC for people with the mutations at codon 103 on their resistance test.

### Doctor

Truvada is the combined formulation of Viread and Emtriva, given as a single pill once daily. —Ross Slotten, MD

### Activist

Gilead's entry in the combination pill parade, FTC/tenofovir has shown it can outperform the old stalwart AZT/3TC combo—in no small part thanks to fewer side effects, but impressive, nonetheless. Given that Truvada is the equivalent of taking FTC and tenofovir separately—same side effects, doses and effectiveness—its distinctions are of the "one less" variety, as in one less pill and one less drug co-pay. It's long intracellular half-life will be attractive to people looking for a once daily regimen with (hopefully) more cushion, but other factors—impact of developing resistance, drug interactions, kidney stress—cannot be ignored. The combination of FTC, tenofovir and efavirenz—all once daily drugs with long half-lives—has all the makers excited enough to cross company walls and put the three together in one pill. Look for it in the coming year. Can't wait to see the name on that one…. —Heidi M. Nass

**Brand Name:** Viramune

**Common Name:** nevirapine (NVP)

## One 200 mg tablet twice daily

**Class:** non-nucleoside analog (also called non-nucleoside reverse transcriptase inhibitor, NNRTI, or non-nuke)

**Standard dose:** One 200 mg tablet daily for two weeks, then full dose of one 200 mg tablet twice daily; frequently prescribed as two 200 mg tablets once a day, although once-daily dosing is not FDA-approved.

**AWP:** $413.24 / month

**Manufacturer contact:** Boehringer-Ingelheim, www.viramune.com, 1 (800) 274–8651

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Most common side effects include headache, nausea, vomiting and rash. The reason for the 14-day lead-in dosing is to reduce the frequency of rash and incidence of drug-induced hepatitis. A serious side effect of the NNRTI class is rash, which can be life-threatening. If you experience blistering, mouth sores, conjunctivitis (redness or inflammation of eye, or pink eye, which if untreated may result in permanent vision loss), swelling, muscle or joint aches, fever or general malaise (general ill feeling), stop taking Viramune and your other anti-HIV meds and seek immediate medical attention.

Do not increase dose if rash develops during dose escalation or if you develop any rash accompanied by the above listed conditions. An increase in liver enzyme levels has been observed and in rare instances the development of hepatitis. May need to stop taking nevirapine until liver function returns to normal. Permanently discontinue if abnormalities return. Although rare, severe and life-threatening skin reactions and hepatotoxicity (liver damage), including fatal cases of each, have occurred.

**Potential drug interactions:** Methadone dose may need to be increased due to withdrawal symptoms. Viramune reduces levels of protease inhibitors. If they are taken at the same time the doses must be increased. Crixivan should be increased to 1,000 mg every eight hours. Kaletra should be increased to four capsules twice-a-day. Viramune interacts with rifampin requiring dose adjustment, but not with Mycobutin (rifabutin). The effectiveness of birth control pills may be decreased when taking Viramune; women and their male partners should consider the use of alternative contraception methods with barrier.

**Tips:** Because of the incidence of rash (9% of any grade through 52 weeks of treatment) associated with Viramune, examine yourself thoroughly for the slightest sign of rash. Notify your doctor of any rash, even mild. Rash may be avoided by using dose escalation schedule. Women may be at higher risk for rash. Use of pretreatment, such as prednisone or Benadryl (diphenhydramine), a non-prescription oral antihistamine, may be used to minimize the risk of rash and to control itching but the reaction can actually be worse—discuss it with your healthcare provider. A topical (placed on the skin) hydrocortisone or an oatmeal-containing cream, such as Aveeno, may improve comfort. Topical antihistamine-containing products should be avoided since there have been reports of irritation and rashes spreading. In any case, let your medical provider know you have a rash. Monitor liver function tests during first six months, initially every two weeks. The increased period of risk for liver injury is primarily in the first 6–12 weeks of taking Viramune. Do not ignore yellowing of your eyes or skin, as this may be a sign of a severe liver effect. A package insert warning states that women with more than 250 T-cells have a 12-times greater risk of serious liver side effects, including fatal ones.

Studies show that Viramune crosses the blood-brain barrier to a useful degree, which may be beneficial for patients at risk for neurological damage (such as dementia) from HIV. Viramune has also been shown to have a positive impact on cholesterol and triglycerides levels. When given around the time of labor Viramune has demonstrated effectiveness in preventing the transmission of HIV from mother to child, but there was an increase in HIV drug resistance in the moms. Single or double dose Viramune may be used for babies born to HIV-positive mothers.

### Doctor

Viramune is a potent NNRTI, probably equivalent in all ways to Sustiva. Its main drawbacks are some potentially serious side effects. A rash occurs in more than 10% of patients, occasionally progressing to a severe reaction known as the Stevens-Johnson syndrome, which can be fatal. Another 10% may develop a chemical hepatitis from Viramune, which also can be fatal. In the majority of people it is well tolerated; and, like Sustiva, it can be dosed once daily. It has been effective in preventing maternal-fetal transmission of HIV; and it penetrates the blood-brain barrier, making it a good choice for patients with neurological symptoms of HIV/AIDS. Adherence with Viramune is critical: if a person develops resistance to Viramune, he or she will become resistant to the entire class of current NNRTIs. —Ross Slotten, MD

### Activist

Nevirapine came on the scene as the first NNRTI, only to be overshadowed a few years later by the potent, once-daily efavirenz. It didn't retreat quietly to the shelves, however. BI took it head-to-head with efavirenz and showed it could compete, and was easier on lipids, to boot. One dose of nevirapine has reduced transmission to babies at birth, only to confer NNRTI resistance to the mothers. Adding a few days of AZT/3TC could prevent resistance and preserve future options. On a related note, nevirapine must be stopped carefully—it stays around a lot longer than some drugs, so you may have to quit it before your other ARVs or risk broad NNRTI resistance. Women with more than 250 CD-4 cells or men with more than 400 CD4s thinking of starting neviripine: proceed with caution! The risk of liver toxicity is higher for you. If it gives you a rash (listen up, women), get your liver checked. —Heidi M. Nass

## Two 200 mg tablet three times daily

**Class:** non-nucleoside analog (also called non-nucleoside reverse transcriptase inhibitor, NNRTI or non-nuke)

**Standard dose:** Two 200 mg tablets or four 100 mg tablets three times a day. Only the 100 mg tablets can be dissolved in liquid, however avoid grapefruit juice; no food restrictions (may be taken with or without food). Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $316.35 / month for 200 mg

**Manufacturer contact:** Agouron Pharmaceuticals, a Pfizer company, www.pfizer.com, 1 (888) 777–6637

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Most common side effects include headache, nausea, vomiting, diarrhea, fatigue, elevated liver enzymes, itchy skin or rash. A serious side effect of the NNRTI class is rash, which can be life-threatening. If you experience blistering, mouth lesions, conjunctivitis (redness or inflammation of eye, which if untreated may result in permanent vision loss), swelling, muscle or joint aches, fever or general malaise (general ill feeling), stop taking Rescriptor and seek immediate medical attention.

**Potential drug interactions:** You cannot take the following medications with Rescriptor: Versed (midazolam), Halcion (triazolam) and Xanax (alprazolam), pimozide (a psychiatric medication), ergot alkaloids (Wigraine and Cafergot) in any form—serious interactions are seen with dilation during gynecological exams. Do not use Zocor (simvastatin) or Mevacor (lovastatin) cholesterol (lipid) lowering meds; suggested alternatives are Lipitor (atorvastatin), Lescol (fluvastatin), and Pravachol (pravastatin, the one with less incidence of problems and interactions according to study data). Liver enzymes should be checked regularly if you are on these cholesterol meds, as they can increase risk for liver toxicity with Rescriptor. Certain amphetamines and antiarrhythmic drugs should not be used with Rescriptor, therefore inform your healthcare provider if you have a history of heart or blood pressure problems. Potential toxicity when given with Biaxin (clarithromycin), dapsone, Mycobutin (rifabutin), Procardia (nitedipine), Coumadin (warfarin) and quinidine. Tegretol (carbamazepine, an anti-seizure medication used to treat peripheral neuropathy), phenobarbital, Dilantin (phenytoin), Mycobutin (rifabutin) and rifampin (used to treat tuberculosis) are drugs that decrease Rescriptor levels. Rescriptor increases levels of Crixivan, Fortovase, Invirase, Kaletra, Reyataz and methadone.

**Tips:** Research demonstrates smaller doses of Rescriptor increases blood levels of some protease inhibitors, making it unique among the NNRTIs. Videx (not Videx EC), antacids (like Tagamet, Zantac and Tums) and gastric achlorhydria (low stomach acid) decreases absorption of Rescriptor, so take at least one hour apart from these drugs and from acidic beverages such as orange or cranberry juice. Do not use herbal preparations, such as St. John's wort, without checking with your healthcare provider or pharmacist.

### Doctor

Delavirdine is an NNRTI given three times daily, limiting its usefulness. Its resistance pattern is similar to that of Viramune and Sustiva and therefore it has no role in salvage therapy. —Ross Slotten, MD

### Activist

Maybe timing really is everything. Delavirdine was approved after the first drug in its class, nevirapine. Unfortunately, it wasn't as potent, had a more difficult dosing schedule, and came with lots of drug interactions. Given how quickly resistance to this whole class can develop with the failure of one NNRTI, why would anyone blow their NNRTI wad on delavirdine? The U.S. guidelines don't recommend it as a first-line agent; the European drug approval agency just said "no" to delavirdine, period. Because it inhibits a particular pathway in the liver (which is what leads to so many drug interactions), it can raise the levels of some protease inhibitors. If you need to boost your PI and you can't tolerate the usual booster, ritonovir, and you're already resistant to the NNRTIs, well, does Agouron have the drug for you! —Heidi M. Nass

**Brand Name:** Sustiva

**Common Name:** efavirenz (EFV)

## One 600 mg tablet once daily


**Class:** non-nucleoside analog (also called non-nucleoside reverse transcriptase inhibitor, NNRTI or non-nuke)

**Standard dose:** One 600 mg tablet, typically at bedtime; with a light snack or 30 minutes after food. Also available in smaller 50 mg, 100 mg and 200 mg capsules. Dose can be split up. Approved for children 3 years and older. Strawberry/mint flavored solution available to children under expanded access program. Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $473.70 / month

**Manufacturer contact:** Bristol-Myers Squibb, www.sustiva.com; 1 (800) 334–4486

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Because Sustiva penetrates so readily into the brain, up to 50% of patients experience some kind of central nervous system (CNS) symptoms (dizziness, headache, somnolence or hypnotic trance). Psychiatric symptoms (confusion, insomnia, hallucinations, vivid dreams or nightmares, depression, euphoria or mania, agitation) are less frequent. Some people in recovery from substance use will experience flashbacks. Other side effects include rash, nausea, vomiting, diarrhea, fever, insomnia and increased liver enzymes. These symptoms occur early and generally resolve within two to four weeks. If you can't sleep (which more commonly develops after some time on Sustiva), ask about switching the timing of your dose little by little until you're taking it in the daytime. A serious side effect of the NNRTI class is rash, which can be life-threatening. If you experience blistering, mouth lesions, conjunctivitis (redness or inflammation of eye, which if untreated may result in permanent vision loss), swelling, muscle or joint aches, fever or general malaise (general ill feeling), stop taking Sustiva and seek immediate medical attention. Rash is more common, and more severe, in children, as is diarrhea, fever and low levels of some blood cells. May raise levels of triglycerides and the good cholesterol (HDL). May lead to false positive tests for use of marijuana. Women taking Sustiva should not become pregnant or breast-feed because of the risk of birth defects.

**Potential drug interactions:** You cannot take the following medications with Sustiva: Versed (midazolam), Halcion (triazolam), or ergot medications (Wigraine and Cafergot), in any form—serious interactions seen with dilation during gynecological exams. Do not use with Biaxin (clarithromycin), as levels of Biaxin are reduced. May affect Coumadin (warfarin) therapy. Dosing adjustment may be necessary for people on methadone due to withdrawal symptoms. When taken with Sustiva, Crixivan should be increased to 1,000 mg every eight hours or it should be boosted with Norvir, and increase Kaletra to four capsules twice daily. Reyataz should also be "boosted" with Norvir (Reyataz 300 mg/Norvir 100 mg), still once daily, when taken with Sustiva. Sustiva and saquinavir (Fortovase and Invirase) should not be used in combination, because levels of saquinavir are decreased substantially. No interaction data available with Fortovase/Norvir—consider doubling Fortovase to 800 mg twice-a-day. Monitor liver enzymes closely if Sustiva and Norvir are used together due to potential risk of liver damage. With once-daily Lexiva, boost with 300 mg Norvir.

**Tips:** Women of child-bearing age and their male partners should consider the use of alternative contraception methods with barrier, in addition to the Pill, because of the potential for embryo heart defects. It is recommended that Sustiva be taken at bedtime to help reduce CNS symptoms, but can be taken at any time. People have described having "happy dreams" or nightmares depending on their mood or types of movies (Disney movie or horror movie, for example) or television shows they viewed before sleep. Avoid driving or operating heavy machinery for a few hours after dose. Side effects may linger. Taking Sustiva with high-fat food may increase the body's uptake of Sustiva, and alcohol may increase blood concentrations—both could up the risk of experiencing side effects. Some people adjust to Sustiva when taking Ativan or Ambien to sleep for the first few weeks, but either may make you even more groggy the next morning. Some people develop sleeplessness and increased energy after taking Sustiva. If this happens, you may try taking it when you wake up. Shown to penetrate lymphoid tissue, a hiding place for HIV. A genetic predisposition to having Sustiva clear out of your body more slowly—and thereby increasing your side effects—was seen more often in African Americans than in whites (20% vs. 3%).

### Doctor

Sustiva is the quintessential NNRTI. Its potency and durability have withstood the test of time: Sustiva appears on everyone's list as a first-line therapy against HIV. Unlike Viramune, Sustiva has no dangerous side effects. It can cause a rash, which is rarely severe and resolves spontaneously. It also can elevate total cholesterol levels, though LDL levels (the "bad" cholesterol) usually are significantly affected. So-called neuropsychiatric side effects are the most annoying drawback to Sustiva. In the first few days of therapy, the patient may feel stoned; but this feeling dissipates quickly. More disturbing are the vivid dreams, which are intolerable to some people, especially those prone to mood disorders, like depression and bipolar disorder. Sometime in 2005 or 2006, Sustiva will be co-formulated with Truvada (Viread and Emtriva) into a single tablet, given once daily. —Ross Slotten, MD

### Activist

When efavirenz first came out I thought all the potential CNS effects sounded freaky. Fighting HIV now included bad dreams, dizziness and sleep problems? It seemed like too much to ask. Plenty of people weren't so put off, though, and it has become a very popular drug. A potent drug for a once-daily regimen with few pills and no food required—gee, can't imagine why it's a favorite. Of the two "preferred" agents recommended in the federal guidelines for people starting their first regimen (with two NRTIs), one is a PI and the other is efavirenz. People sail along on efavirenz, but for people with underlying depression—diagnosed or not—check yourself before you wreck yourself. Make sure your mood isn't slipping. Note that it can harm a fetus in early development, so it is not recommended for pregnancy. Also, mind your lipids—efavirenz taught us that raising cholesterol and triglycerides isn't just for PIs. —Heidi M. Nass

## Five 200 mg capsules + 100 mg Norvir twice daily

**Class:** HIV protease inhibitor (PI)

**Standard dose:** Five 200 mg hard-gel capsules + Norvir 100 mg two times a day with food, or within two hours after a meal. Cannot be taken without Norvir. Take a missed dose as soon as possible, but do not double up on your dose. (New 500 mg formulation available soon.)

**AWP:** $646.96 / month for 200 mg

**Manufacturer contact:** Roche Pharmaceuticals, www.rocheusa.com, 1 (800) 910–4687

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Most common are stomach related: diarrhea, abdominal discomfort and nausea. Because there is low absorption (4 to 6%) of the drug into the body, there are few other side effects. As seen with all other protease inhibitors are increased levels of cholesterol and triglycerides, except possibly unboosted Reyataz (atazanavir) and these increased levels may be associated with heart disease. Other possible side effects are lipodystrophy (body fat changes, including thinning of the face, arms and legs, with or without fat accumulation in the stomach, breasts and sometimes the upper back), onset of new cases or worsening of diabetes (see your doctor promptly) and increased bleeding in hemophiliacs.

**Potential drug interactions:** Do not take with Tambocor (flecainide), Rythmol (propafenone), Versed, Halcion, Hismanol, Seldane, rifampin, ergot derivatives (such as Cafergot, Wigraine and Methergine, D.H.E. 45, in any form—serious interactions seen with dilation during gynecological exams), garlic supplements, or the herb St. John's wort. Do not use Zocor (simvastatin) or Mevacor (lovastatin); lipid-lowering alternatives are Lipitor (atorvastain), Lescol, and Pravachol (parvastatin), but they should be used with caution due to potential for liver toxicity.

Viramune, Sustiva and Mycobutin (rifabutin) decreases Invirase levels. Invirase may increase dapsone levels. Antifungal Nizoral (ketoconazole) or Sporonox (itraconazole), used for treatment of candidiasis (thrush), increases the amount of Invirase in the body. Do not take with birth control pills; Invirase reduces level of ethinyl estradiol by 40%. Prescriber may need to adjust doses accordingly. Rescriptor, Crixivan, Norvir, Viracept and Kaletra all significantly increase Invirase's concentrations. No dosage change when taken with Kaletra.

Protease inhibitors increase blood levels of Viagra (sidenafil citrate), Cialis (tadalafil) and Levitra (vardenafil). Use with caution. Initially the Viagra dose should be 12.5 mg (½ of 25 mg tablet) and increased as needed and tolerated. It's recommended that people on PIs do not exceed 25 mg of Viagra in a 48-hour period because of potential for serious reaction. Use Cialis at reduced doses of 10 mg every 72 hours and Levitra at reduced doses of no more than 2.5 mg every 72 hours, with increased monitoring for adverse events.

**Tips:** Invirase, the first HIV protease inhibitor out on the market, has made a comeback, due to study results indicating strong efficacy with fewer side effects when taken with a mini-dose of Norvir, as compared to Fortovase/Norvir. It has the considerable advantage of less diarrhea, vomiting and abdominal distension compared with Fortovase plus Norvir. Invirase/Norvir has demonstrated A1 safety and efficacy (the highest category rating) according to U.S. HIV treatment guidelines. This oldie is a goodie. Must be taken with food. There is also some research supporting Invirase 1000 mg + Kaletra standard dose twice-a-day.

### Doctor

Saquinavir was the first protease inhibitor, approved in 1995. Formulated as a hard gel capsule (Invirase), saquinavir was not well absorbed, making it less potent than later PIs. However, its effectiveness improved dramatically when it was co-administered with Norvir. A later soft-gel version (Fortovase) also improved absorption. Side effects are few, though diarrhea is the most common complaint. The pill burden of unboosted saquinavir will intimidate all but the bravest—6 capsules three times a day or nine capsules twice a day! When it is finally reformulated into a smaller number of pills, it may one day compete favorably with other PIs. —Ross Slotten, MD

### Activist

In HIV treatment there's the same phenomenon as in fashion—everything old is, eventually, new again. In its original hard-gel form, saquinavir had the distinction of being the first protease inhibitor but little else to distinguish it…unless you count a difficult dosing schedule, lots of gut effects, and poor absorption. It faded into the wings when its soft-gel version came to market, only to reappear as the favored saquinavir formulation for use with a ritonavir boost. Ritonavir ups saquinavir exposure, but it can add a layer of gut distress, too. It has also been paired with Kaletra in what tends toward a sledgehammer approach to fighting heavily resistant HIV–cobble together a regimen with the most antiviral power you can find and overcome resistance with sheer brute force …limited only by what one gut can handle. Roche's new 500 mg. tablet will cut the pill burden by more than half. —Heidi M. Nass

**Brand Name:** Invirase

**Common Name:** saquinavir hard-gel (SQV-HGC)

**Brand Name:** Crixivan

**Common Name:** indinavir sulfate

## Two 400 mg capsules every eight hours

**Class:** HIV protease inhibitor (PI)

**Standard dose:** Rarely used by itself (two 400 mg capsules every eight hours with no food or a low-fat snack). Almost always boosted with Norvir: 400 mg Crixivan + 400 mg Norvir BID; 800 mg + 100 mg BID; or 800 mg + 200 mg BID (all combination doses taken with food, and with plenty of water to avoid kidney sludge or stones). Take a missed dose as soon as possible, but do not double up on your dose. Also available in 100 mg, 200 mg and 333 mg capsules.

**AWP:** $557.26 / month for 400 mg, 180 capsules

**Manufacturer contact:** Merck and Co., www.crixivan.com, 1 (800) 850–3430

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Potential side effects include: headache, fatigue or weakness, malaise (general ill feeling), nausea, diarrhea, stomach pains, loss of appetite, yellowing of skin/eyes, changed skin color, dry mouth/sore throat, taste changes, painful urination, indigestion, joint pain, hives, and liver toxicity. Itchy/dry skin, ingrown toe nails and hair loss are unique to Crixivan. Kidney stones, which may lead to more serious problems, can also occur. If pain develops in the middle to lower stomach or the back, or if there is blood in the urine call your healthcare provider immediately. Drugs such as Bactrim and Dapsone are associated with hemolytic anemia, so be careful when using indinavir. Hemolytic anemia is the fast breakdown of red blood cells. It is rare but can lead to severe problems—monitoring red blood counts is necessary. An increase in bilirubin (a test of liver function) has been reported, but it is not associated with liver problems. It may sometimes cause yellowing of the skin or eyes. As seen with all other protease inhibitors are increased levels of cholesterol and triglycerides, except possibly unboosted Reyataz (atazanavir) and these increased levels may be associated with heart disease. Other possible side effects are lipodystrophy (body fat changes, including thinning of the face, arms and legs, with or without fat accumulation in the stomach, breasts and sometimes the upper back), onset of new cases or worsening of diabetes (see your doctor promptly) and increased bleeding in hemophiliacs.

**Potential drug interactions:** Do not take with Tambocor (flecainide), Rythmol (propafenone), Versed, Halcion, Hismanol, Seldane, rifampin, pimozide (a psychiatric drug), ergot derivatives (such as Cafergot, Wigraine and Methergine, D.H.E. 45, in any form—serious interactions seen with dilation during gynecological exams), garlic supplements, or the herb St. John's wort. Do not use Zocor (simvastatin) or Mevacor (lovastatin); lipid-lowering alternatives are Lipitor (atorvastain), Lescol, and Pravachol (pravastatin), but they should be used with caution due to potential for liver toxicity.

Increase Crixivan to 1,000 mg every eight hours when taken with Viramune or Sustiva, or take Crixivan boosted by Norvir. Not recommended in combination with Reyataz. Reduce Crixivan to 600 mg every eight hours when taken with Rescriptor. Reduce Crixivan to 600 mg every eight hours when taken with Sporanax (itraconazole, 200 mg twice-a-day) or Nizoral (ketoconazole, 200 mg once-a-day) or ketoconazole.

The dose of rifampin (Mycobutin) should be reduced by 50% and increase Crixivan dose to 1000 mg every eight hours when taken together.

Protease inhibitors increase blood levels of Viagra (sidenafil citrate), Cialis (tadalafil) and Levitra (vardenafil). Use with caution. Initially the Viagra dose should be 12.5 mg (½ of 25 mg tablet) and increased as needed and tolerated. It's recommended that people on PIs do not exceed 25 mg of Viagra in a 48-hour period because of potential for serious reaction. Use Cialis at reduced doses of 10 mg every 72 hours and Levitra at reduced doses of no more than 2.5 mg every 72 hours, with increased monitoring for adverse events.

**Tips:** Combining PIs continues to be a common practice today—some combinations with lower doses of Crixivan include: Crixivan 1200 mg with 1250 Viracept each twice-a-day; and Crixivan 600 mg with standard dose of Kaletra each twice-a-day. It is recommended that you drink at least 48 oz fluids daily, preferably water or clear liquids (soda pop doesn't count!) to decrease the chances of a kidney stone forming. Don't forget to drink more water in summer or with increased sweating. Large amounts of coffee or alcohol can increase risk of stones due to increased dehydration. Stones may continue after stopping Crixivan. Grapefruit juice decreases Crixivan blood levels. Should be stored in original container and kept dry.

### Doctor

Crixivan, once the darling of anti-HIV regimens, has faded in popularity since the development of less finicky PIs. Unboosted, it must be given three times a day on an empty stomach. Moreover, it must be taken with large quantities of water because of the risk of kidney stones (crystallized Crixivan). Boosting Crixivan with Norvir eliminates the dietary restrictions, but not the frequency of stones. It was once blamed as the cause of the lipodystrophy syndrome ("Crix belly"); but at the time it was the most commonly prescribed anti-HIV medication. Subsequent studies have exonerated Crixivan—or at least spread around the blame—demonstrating that other drugs are also associated with the syndrome. —Ross Slotten, MD

### Activist

Indinavir got associated with lipodystrophy early. Before lipodystrophy had a name, it was referred to in the community as "Crix belly". It was a bad rap—not because it didn't play a role in the body shape changes we started seeing after HAART became the standard, but because it wasn't the lone culprit. Indinavir started out as 2 capsules every 8 hours with *lots* of water and no food; now it's a few capsules twice a day with a meal, thanks to the ever-popular—say it with me—ritonavir boost. Like the other PIs left in Kaletra's wake, it's boost or bust for indinavir. —Heidi M. Nass

## Six 100 mg capsules twice daily

**Class:** HIV protease inhibitor (PI)

**Standard dose:** Almost never used at its approved dose (a lead-in dosing, then six 100 mg soft gelatin capsules twice-a-day, preferably with food—dose escalation is important to avoid side effects). Norvir is primarily used as a boosting agent for other PIs, at smaller doses of 100 to 400 mg, either once or twice a day. Take a missed dose as soon as possible, but do not double up on your dose. Approved for children ages 2 and older. Liquid formula available, but tastes unbelievably horrific.

**AWP:** $1,285.89 / month for 120 capsules

**Manufacturer contact:** Abbott Laboratories, www.norvir.com, 1 (800) 222–6885

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Most common side effects include: weakness, stomach pain, upset stomach (nausea, diarrhea, and vomiting), tingling/numbness around the mouth, hands or feet, loss of appetite, taste disturbance, weight loss, headache, dizziness, pancreatitis (see nukes), and alcohol intolerance.

As seen with all other protease inhibitors are increased levels of cholesterol and triglycerides, except possibly unboosted Reyataz (atazanavir) and these increased levels may be associated with heart disease. Other possible side effects are lipodystrophy (body fat changes, including thinning of the face, arms and legs, with or without fat accumulation in the stomach, breasts and sometimes the upper back), onset of new cases or worsening of diabetes (see your doctor promptly) and increased bleeding in hemophiliacs.

Other potential side effects are liver problems, such as increase in liver enzymes (AST, ALT and GGT), hepatitis, or jaundice (yellowing of skin); and increased muscle enzyme (CPK) and uric acid. People with hepatitis B or C may be at increased risk.

**Potential drug interactions:** Ritonavir interacts with *many* other drugs. See the manufacturer package insert for the most complete list. Do not take with Tambocor (flecainide), Rythmol (propafenone), Versed, Halcion, Hismanol, Seldane, rifampin, ergot derivatives (such as Cafergot, Wigraine and Methergine, D.H.E. 45, in any form—serious interactions seen with dilation during gynecological exams), Antabuse or Flagyl, garlic supplements, or the herb St. John's wort. Do not use Zocor (simvastatin) or Mevacor (lovastatin); lipid-lowering alternatives are Lipitor (atorvastatin), Lescol, and Pravachol (pravastatin), but they should be used with caution due to potential for liver toxicity.

Protease inhibitors increase blood levels of Viagra (sildenafil citrate), Cialis (tadalafil) and Levitra (vardenafil). Use with caution. Initially the Viagra dose should be 12.5 mg (½ of 25 mg tablet) and increased as needed and tolerated. It's recommended that people on PIs do not exceed 25 mg of Viagra in a 48-hour period because of potential for serious reaction. Use Cialis at reduced doses of 10 mg every 72 hours and Levitra at reduced doses of no more than 2.5 mg every 72 hours, with increased monitoring for adverse events.

Levels of the street drug Ecstasy are greatly increased by Norvir, and at least one death has been attributed to the combination. GHB is also dangerous with Norvir. Tobacco and alcohol may lower blood levels of Norvir. Increases seen in clarithromycin (Biaxin) levels by 80 percent. Rifampin decreases Norvir levels by 35 percent. Contains alcohol (but should not be enough to trigger relapse) and greatly hastens intoxication.

**Tips:** The real strength of Norvir is in combination with other PIs (used as a boosting agent), allowing for a lower dose of both. Stomach side effects are reduced by taking Norvir with high fat foods (such as peanut butter or avocado)—however, be careful because some other HIV medicines should not be taken with high fat foods. You can mix liquid solution in ice cream, milk or pudding to hide the bitter taste. Capsules do not need refrigeration if stored below 77° F and used within 30 days, but keep them tightly sealed in original container. The capsules contain castor oil and have bitter taste. Chocolate masks the bitter taste. Plasma concentration increases in people with hepatic (liver) impairment.

### Doctor

Norvir is no longer used as a single PI because patients are unable to tolerate therapeutic doses. However, as a boosting agent it has found its niche, vastly improving the potency, and diminishing the pill burden, of other PIs. —Ross Slotten, MD

### Activist

Talk about a comeback. Ritonavir went from an impossible PI on its own—12 capsules a day and gut-wrenching side effects—to a boosting agent in what seems like virtually every PI-based regimen out there, albeit at a fraction of the dose. Speaking of fractions, last year Abbott raised the price of ritonavir by four times what it was. Let's do the math: nobody uses the original dose of 1,200 mg a day but lots of people use 200, or maybe 400 mg a day—about one-fourth the original dose, more or less. So, ¼ dose x 400% price increase = problem solved…and one irate community. The ritonavir boost is a good news/bad news deal: the potency kick is really good and valuable; the impact on lipids, gut distress and interaction with other drugs can be a buzz wrecker. No free lunch, indeed. —Heidi M. Nass

**Brand Name:** Viracept

**Common Name:** nelfinavir

## Two 625 mg tablets twice daily


**Class:** HIV protease inhibitor (PI)

**Standard dose:** Two 625 mg tablets (or five 250 mg tablets) twice-a-day with food. Take a missed dose as soon as possible, but do not double up on your dose. Viracept Oral Powder also available for children and individuals unable to swallow tablets.

**AWP:** $756.66 / month for 625 mg

**Manufacturer contact:** Agouron Pharamaceuticals, a Pfizer company, www.viracept.com, 1 (888) 777–6637

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Most common include: diarrhea (15-20% of patients in Study 542), stomach discomfort, nausea, gas, weakness and rash.

As seen with all other protease inhibitors are increased levels of cholesterol and triglycerides, except possibly unboosted Reyataz (atazanavir) and these increased levels may be associated with heart disease. Other possible side effects are lipodystrophy (body fat changes, including thinning of the face, arms and legs, with or without fat accumulation in the stomach, breasts and sometimes the upper back), onset of new cases or worsening of diabetes (see your doctor promptly) and increased bleeding in hemophiliacs.

**Potential drug interactions:** In general, less severe interactions compared to other drugs in this class.

Do not take with Tambocor (flecainide), Rythmol (propafenone), Versed, Cordarone (amiodarone), Halcion, Hismanol, Seldane, rifampin, ergot derivatives (such as Cafergot, Wigraine and Methergine, D.H.E. 45, in any form—serious interactions seen with dilation during gynecological exams), garlic supplements, or the herb St. John's wort. Do not use Zocor (simvastatin) or Mevacor (lovastatin); lipid-lowering alternatives are Lipitor (atorvastain), Lescol, and Pravachol (pravastatin), but they should be used with caution due to potential for liver toxicity. Rifampin and Viracept should not be used together.

Blood levels of Viracept are reduced by rifampin and may be reduced by phenobarbital, phenytoin, and carbamazepine (Tegretol and others). Fortovase levels increase three-to-five-fold, Crixivan increases 50% (see Crixivan for potential drug interactions). Mycobutin (rifabutin) dose must be decreased when used with Viracept. Prescriber may need to adjust doses of any of these drugs accordingly.

Protease inhibitors increase blood levels of Viagra (sidenafil citrate), Cialis (tadalafil) and Levitra (vardenafil). Use with caution. Initially the Viagra dose should be 12.5 mg (½ of 25 mg tablet) and increased as needed and tolerated. It's recommended that people on PIs do not exceed 25 mg of Viagra in a 48-hour period because of potential for serious reaction. Use Cialis at reduced doses of 10 mg every 72 hours and Levitra at reduced doses of no more than 2.5 mg every 72 hours, with increased monitoring for adverse events.

The effectiveness of birth control pills may be decreased when taking Viracept; women and their male partners should consider the use of alternative contraception methods with barrier.

**Tips:** Do not leave pharmacy without anti-diarrhea meds such as Immodium, Tums or other calcium products. Taking a 500 mg calcium supplement with doses hugely decreases diarrhea. Also try Solgar oat bran tablets, psyllium husk fiber bars and pancreatic enzymes (all with meals). As an extra precaution, take a change of clothes with you everyday for the first several weeks—stick it out, most often symptoms improve after two or three weeks. The oral powder tastes horrible and requires a large amount for mixing into food. Patients can crush adult tablets for use in children or dissolve tablets in a small amount of water. Acidic food or juice (e.g. orange/apple juice or apple sauce) not recommended in combination with Viracept, due to resulting bitter taste. To get the full benefit of Viracept by increasing its level in the body, it must be taken with a meal of at least 500 calories, with at least 20% to 50% of those calories coming from fat. Examples of meals that help to get to adequate food intakes include: Taco Bell Breakfast Burrito and 8 oz of non-acid juice (650 calories, 35% from fat) or Subway Tuna Sandwich including potato chips and 8 oz of skim milk (703 calories, 41% from fat).

### Doctor

Viracept at one time surpassed Crixivan as the most commonly prescribed PI. Today, it has been surpassed by other PIs. However, when it was first marketed, it could be taken with food, a distinct advantage over Crixivan. Moreover, the Crixivan-associated kidney stones were not a problem. Once prescribed three times daily, studies demonstrated that it could be given twice a day. Its main drawback is diarrhea, which can be explosive and unpredictable. In head-to-head trials with other PIs, Viracept appears to be less potent which, along with its annoying gastrointestinal side effect, has contributed to its decline in use. —Ross Slotten, MD

### Activist

Anecdotally, people say the new formulation is easier on the gut than the old one. On the face of it, that's not saying much—the old one was b-a-d—but people really seem to tolerate the 625 mg pills much better. In my years with nelfinavir, I pretty much mastered the gut issues; it was the lipid kick that did me in. Its impact on blood fats doesn't set it apart from most other PIs, but it must be considered if long-term survival, sans heart attacks, is the goal. Regarded as a potency weakling, it's used like a sparring partner for other PIs in studies. Companies pit their new drugs against nelfinavir in what amounts to a lame "at least we're no worse than the weakest one!" trial design. It's a recommended agent for use in pregnancy and it may get a second life in the world of double PI therapy, so don't count it out. —Heidi M. Nass

## Six 200 mg capsules three times daily

**Class:** HIV protease inhibitor (PI)

**Standard dose:** Six 200 mg soft-gel capsules three times a day with food, or within two hours after a meal; or five 200 mg Fortovase with 100 mg Norvir, twice-a-day with food. Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $257 / month

**Manfacturer contact:** Roche Pharmaceuticals, www.fortovase.com, 1 (800) 910–4687

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Most common include diarrhea, nausea, stomach pain, gas, indigestion, vomiting, headaches, insomnia, fatigue, body aches, anxiety, depression and taste alteration.

As seen with all other protease inhibitors are increased levels of cholesterol and triglycerides, except possibly unboosted Reyataz (atazanavir) and these increased levels may be associated with heart disease. Other possible side effects are lipodystrophy (body fat changes, including thinning of the face, arms and legs, with or without fat accumulation in the stomach, breasts and sometimes the upper back), onset of new cases or worsening of diabetes (see your doctor promptly) and increased bleeding in hemophiliacs.

**Potential drug interactions:** Do not take with Tambocor (flecainide), Rythmol (propafenone), Versed, Halcion, Hismanol, Seldane, rifampin, ergot derivatives (such as Cafergot, Wigraine and Methergine, D.H.E. 45, in any form—serious interactions seen with dilation during gynecological exams), garlic supplements, or the herb St. John's wort. Do not use Zocor (simvastatin) or Mevacor (lovastatin); lipid-lowering alternatives are Lipitor (atorvastatin), Lescol, and Pravachol (pravastatin), but they should be used with caution due to potential for liver toxicity. Rifampin and Fortovase should not be used together.

Increased blood levels when taken with Crixivan, Norvir and Viracept. Blood levels are decreased significantly by Sustiva and Viramune, but can be taken together if Norvir is included. Other drugs that may also reduce Fortovase blood levels are Decadron and Tegretol, Dilantin, and phenobarbital. High incidence of liver problems, and severe ones, when taken with Rescriptor. The side effects of calcium channel blockers, clindamycin, dapsone and quinidine may be increased if taken with saquinavir.

Protease inhibitors increase blood levels of Viagra (sildenafil citrate), Cialis (tadalafil) and Levitra (vardenafil). Use with caution. Initially the Viagra dose should be 12.5 mg (½ of 25 mg tablet) and increased as needed and tolerated. It's recommended that people on PIs do not exceed 25 mg of Viagra in a 48-hour period because of potential for serious reaction. Use Cialis at reduced doses of 10 mg every 72 hours and Levitra at reduced doses of no more than 2.5 mg every 72 hours, with increased monitoring for adverse events.

**Tips:** Must be taken with food or within two hours after a meal. Keep capsules at room temperature if they will be used up within three months. Zantac, Pepcid, Tagamet or antacids may be necessary to treat Fortovase heartburn (which is common). Refrigerated (36–46° F or 2–8° C) capsules remain stable until the expiration date printed on the manufacture bottle. Once brought to room temperature capsules should be used within 3 months. Avoid direct sunlight. Dosings of Fortovase boosted with Norvir—five 200 mg Fortovase with one 100 mg Norvir twice-a-day or eight 200 mg Fortovase with one 100 mg Norvir once-a-day or five 200 mg Fortovase with three 133 mg Kaletra (lopinavir/ritonavir) twice-a-day.

### Doctor

Saquinavir, the first protease inhibitor approved by the FDA, comes in two versions: Invirase (soft-gel) and Fortovase (hard-gel). Fortovase has better bioavailability—that is, more of it is absorbed after ingestion. With better absorption, there are more side effects, mainly diarrhea. Recently, however, Invirase has made a comeback because it has fewer side effects, even when combined with Norvir, which significantly boosts blood levels. When taken alone, Fortovase must be given in whopping doses, six pills three times daily! If boosted with Norvir it can be taken in smaller quantities; but diarrhea remains a problem for some people.—Ross Slotten, MD

### Activist

More than once, I've watched the eyes of people making their first treatment decision fill with terror when they look at the HIV drug chart for the first time. Usually, their gaze has fallen on Fortovase and its ant parade of 18 big, shiny capsules (the daily dose!). To add to its charms, it lacks potency on its own, has a reputation for gut disturbance, is dosed every eight hours—shall I go on? Last year it was approved for twice daily dosing at 1,000 mg, with 100 mg of ritonavir. Whew. This reduces pill count, of course, but makes GI matters worse. If you use this drug do an inventory of the other medications you take—the list of possible drug interactions covers a lot of ground. One place Fortovase actually comes recommended is in pregnancy—it's one of two PIs listed in the U.S. treatment guidelines as recommended agents. —Heidi M. Nass

**Brand Name:** Agenerase

**Common Name:** amprenavir

1200 mg twice daily - photo not available

**Class:** HIV protease inhibitor (PI)

**Standard dose:** 1200 mg twice daily. The 150 mg soft gelatin capsules were taken off the market last year because of the new formulation (Lexiva), but the 50 mg capsule remains available. Take missed dose as soon as possible, but do not double up on your next dose.

Approved for children ages 4 and older. Grape, bubblegum, peppermint flavored liquid available. Adults should not use liquid if possible.

**AWP:** $257.19 / month for 50 mg, 480 capsules

**Manufacturer contact:** GlaxoSmithKline, www.treathiv.com, 1 (800) 722–9294

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Most common include: nausea, vomiting, stomach pain, taste disorders, fatigue, headache, mood disorders, anemia and rash. Rash occurred in about 22% of people on Agenerase, but severe rashes were uncommon. If you experience a rash, notify your doctor. For mild or moderate rashes, your doctor may choose to continue Agenerase, with close follow-up and monitoring. Because Agenerase is a sulfonamide, it should be used with caution in patients with allergies to sulfa drugs. Severe rash (see Viramune) and stomach problems (pancreatitis—see NRTIs) while rare, can be severe; notify your healthcare provider immediately.

As seen with all other protease inhibitors are increased levels of cholesterol and triglycerides, except possibly unboosted Reyataz (atazanavir) and these increased levels may be associated with heart disease. Other possible side effects are lipodystrophy (body fat changes, including thinning of the face, arms and legs, with or without fat accumulation in the stomach, breasts and sometimes the upper back), onset of new cases or worsening of diabetes (see your doctor promptly) and increased bleeding in hemophiliacs.

**Potential drug interactions:** Do not take with Tambocor (flecainide), Rythmol (propafenone), Versed, Halcion, Hismanol, Seldane, rifampin, ergot derivatives (such as Cafergot, Wigraine and Methergine, D.H.E. 45, in any form—serious interactions seen with dilation during gynecological exams), garlic supplements, or the herb St. John's wort. Do not use Zocor (simvastatin) or Mevacor (lovastatin); lipid-lowering alternatives are Lipitor (atorvastatin), Lescol, and Pravachol (pravastatin), but they should be used with caution due to potential for liver toxicity. Do not take extra vitamin E.

Rescriptor and Viracept greatly increase Agenerase blood levels (and usually stomach discomfort) and prescriber may need to adjust dose accordingly. Sustiva has been shown to significantly reduce blood levels of Agenerase unless also taken with Norvir.

Other drugs that may be involved in interactions with Agenerase include drugs for your heart (antiarrhythmics, anticoagulants, blood pressure medications, cholesterol medications), drugs for seizures, antibiotics and antifungals, sedatives, steroids, immunosuppresants, drugs for heartburn or acid reflux, oral contraceptives, and antidepressants. If you are taking any of these drugs, be sure to let your doctor and pharmacist know so they can monitor your therapy or make adjustments to your medications.

Protease inhibitors increase blood levels of Viagra (sidenafil citrate), Cialis (tadalafil) and Levitra (vardenafil). Use with caution. Initially the Viagra dose should be 12.5 mg (½ of 25 mg tablet) and increased as needed and tolerated. It's recommended that people on PIs do not exceed 25 mg of Viagra in a 48-hour period because of potential for serious reaction. Use Cialis at reduced doses of 10 mg every 72 hours and Levitra at reduced doses of no more than 2.5 mg every 72 hours, with increased monitoring for adverse events.

**Tips:** On its way to extinction due to new formulation on the market, fos-amprenavir calcium (Lexiva). If you are on Agenerase, you should talk with your doctor about switching to Lexiva. Alternative doses: Agenerase 1200 mg with Norvir 200 mg both once daily; or Agenerase 600 mg with Norvir 100 mg both twice daily. However, you should avoid taking Agenerase with food high in fat, while side effects of Norvir are reduced with food high in fat. Go figure.

May also penetrate the lymph nodes, where virus can hide out. Label warning: Agenerase Oral Solution should not be given to infants and children below the age of 4 years and should not be used by pregnant women because of the propylene glycol amount.

## Doctor

Agenerase, and its related pro-drug formulation, Lexiva, are relative newcomers in the PI field. Like virtually all PIs (or any HIV drug, for that matter), they work very well in treatment-naïve patients. When boosted, they may salvage some patients with multi-drug resistant virus. Agenerase is a huge pill; and it had be taken in handfuls (eight pills twice daily) unless combined with Norvir. The main adverse effect is diarrhea, which is rarely as severe as that caused by Viracept. It can be combined with Kaletra, though it can lower the blood levels of lopinavir, one of the components of Kaletra, thus rendering Kaletra less potent. —Ross Slotten, MD

## Activist

Sometimes it takes a while to get it right, or at least get it better. Six years after Agenerase was approved, GSK came out with the amprenavir pro-drug version, called Lexiva—a significant improvement that pushes Agenerase toward obsolescence. The treatment guidelines don't recommend it—boosted or unboosted—for initial therapy, citing "high pill burden". You know treatment options have gotten better when pill burden is what gets a drug benched. Maybe this drug has a future in the salvage setting if boosted, but it's not likely to be a shining star. Agenerase small talk: each 150 mg capsule—and people used to take 16 of them a day—has 58 times the government's recommended daily allowance of vitamin E. —Heidi M. Nass

## Three capsules twice daily


**Class:** HIV protease inhibitor (PI)

**Standard dose:** Three soft-gelatin capsules (133.3 mg lopinavir and 33.3 mg ritonavir each) twice-a-day, preferably with food; liquid formula available. Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $703.50 / month

**Manufacturer contact:** Abbott Laboratories, www.kaletra.com, 1 (800) 222–6885

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Rash, diarrhea, nausea, vomiting, stomach pain, headache, muscle weakness, increased cholesterol and triglycerides (fats in the blood), and AST/ALT (liver function tests, a sign of liver damage; this may be more common in people with hepatitis B or C).

As seen with all other protease inhibitors are increased levels of cholesterol and triglycerides, except possibly unboosted Reyataz (atazanavir) and these increased levels may be associated with heart disease. Other possible side effects are lipodystrophy (body fat changes, including thinning of the face, arms and legs, with or without fat accumulation in the stomach, breasts and sometimes the upper back), onset of new cases or worsening of diabetes (see your doctor promptly) and increased bleeding in hemophiliacs.

**Potential drug interactions:** Do not take with Versed, Halcion, Hismanol, Seldane, rifampin (Rimactane, Rifadin, Rifater or Rifamate—however, recent studies show that increasing the total daily dose of Kaletra may be an option), ergot derivatives (such as Cafergot, Wigraine and Methergine, D.H.E. 45, in any form—serious interactions seen with dilation during gynecological exams), garlic supplements, or the herb St. John's wort. Do not use Zocor (simvastatin) or Mevacor (lovastatin); lipid-lowering alternatives are Lipitor (atorvastatin), Lescol, and Pravachol (pravastatin), but they should be used with caution due to potential for liver toxicity. Oral solution contains alcohol, so do not use with Antabuse or Flagyl. Also avoid dihydropuridine calcium channel blockers.

Dosage of methadone may need to be increased when taken with Kaletra. Increase Kaletra dose to 4 capsules twice-a-day with food recommended when using with Sustiva or Viramune in people who previously took HIV drugs, especially protease inhibitors. Not recommended to be taken with Lexiva. Kaletra may lower levels of Retrovir and Ziagen. Videx should be given an hour before or two hours after Kaletra, as Kaletra should be taken with food. Mycobutin (rifabutin) dosage should be reduced to 150 mg every other day (or 150 mg three times per week) when used with Kaletra. Phenobarbital, phenytoin (Dilantin and others) or carbamazepine (Tegretol and others) may lower blood levels of Kaletra. Reduces effectiveness of birth control pills; use alternative contraceptive. Mepron levels may be reduced with Kaletra. Avoid Sporanox doses greater than 200 mg per day with Kaletra. People with kidney impairment may require lower Biaxin doses with Kaletra. Transplant medicines like Sandimmune, Gengraf, Neoral, Prograf and Rapamune require close monitoring with Kaletra. Kaletra may alter coumadin levels. Steroids, especially Decadron, may decrease levels of Kaletra.

Protease inhibitors increase blood levels of Viagra (sidenafil citrate), Cialis (tadalafil) and Levitra (vardenafil). Use with caution. Initially the Viagra dose should be 12.5 mg (½ of 25 mg tablet) and increased as needed and tolerated. It's recommended that people on PIs do not exceed 25 mg of Viagra in a 48-hour period because of potential for serious reaction. Use Cialis at reduced doses of 10 mg every 72 hours and Levitra at reduced doses of no more than 2.5 mg every 72 hours, with increased monitoring for adverse events.

**Tips:** See Norvir (ritonavir). Doctors and patients report that Kaletra is very tolerable. Great viral load results out to 5 years in people on their first HIV regimen. Good results also seen in heavily treatment-experienced adults, when compared to Reyataz, even those with protease inhibitor resistance. Use Kaletra with caution in people with mild to moderate hepatic (liver) impairment. The taste may be unappealing due to Norvir. Studies examining strength and durability of once-a-day dosing are ongoing. Kaletra capsules and solution are recommended to be stored in the refrigerator, but they are stable for up to 60 days at room temperature (77 F). However, avoid extreme heat and bright light. A new formulation that doesn't require refrigeration is in the works, especially for resource-poor countries. A once-a-day dose, using a tablet form, is being evaluated. (Using the capsules in a once-daily dosing resulted in a huge increase in side effects.)

### Doctor

Kaletra has rapidly become the most commonly prescribed PI. Studies have demonstrated its high potency; resistance is slow to emerge. It has relatively few side effects besides diarrhea. However, elevated cholesterol can be a problem because Kaletra contains Norvir. The combination of Kaletra and Sustiva, an effective regimen, causes markedly elevated cholesterol levels in 40-50% of patients that may not respond to statins. The risk of coronary artery disease and stroke due to such lipid abnormalities is unclear. Kaletra works well as both a first-line agent and as a component of salvage regimens. —Ross Slotten, MD

### Activist

The big kid on the PI block, thoughts of a PI-based regimen often start and stop with Kaletra. There's no denying its potency—six years of follow-up data demonstrates it convincingly—and scads of people tolerate it just fine. Sometimes, though, I think Abbott forgets you can't take the PI out of Kaletra. Due to the ritonavir boost, it interacts with a lot of drugs (for starters: Viread, hormonal contraceptives, Viagra-type meds), can raise lipids and liver enzymes, can cause gut discomfort, comes as three capsules taken twice a day and wants a pretty good meal to chase. Right now, though, it's all about finding the limits of Kaletra—the company is developing a new formulation to cut pill burden and has asked the government to approve once daily dosing. There's even some convincing, if controversial, data from monotherapy trials. Consider the PI bar raised. —Heidi M. Nass

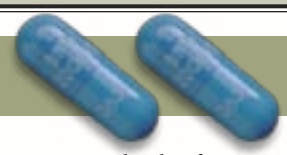
**Brand Name:** Kaletra

**Common Name:** lopinavir/ritonavir

**Brand Name:** Reyataz

**Common Name:** atazanavir sulfate

## Two 200 mg capsules once daily



**Class:** HIV protease inhibitor (PI)

**Standard dose:** Two 200 mg capsules once daily, take with food. Treatment-experienced people should take 300 mg with 100 mg Norvir once daily. Also available in 100 mg and 150 mg capsules. Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $846.92 for 200 mg, 60 capsules

**Manufacturer contact:** Bristol-Myers Squibb, www.reyataz.com, 1 (800) 272–4878

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** Most common include: dizziness and lightheadedness. Elevated levels of unconjugated bilirubin (produced by the liver) was reported in clinical trials in some individuals taking Reyataz. This may result in cases of jaundice (yellowing of the skin or eyes), reported in 7–9% of individuals taking Reyataz. However, no evidence of hepatoxicity (liver problems) was reported. These symptoms usually go away after about two weeks or after you stop taking Reyataz, and seldom return on re-initiation.

All other protease inhibitors are associated with increased levels of cholesterol and triglycerides, except possibly unboosted Reyataz and these increased levels may be associated with heart disease. However, if Reyataz is boosted with Norvir these same changes in cholesterol and triglycerides may occur. Other possible side effects as seen in other PIs are lipodystrophy (body fat changes, including thinning of the face, arms and legs, with or without fat accumulation in the stomach, breasts and sometimes the upper back), onset of new cases or worsening of diabetes (see your doctor promptly) and increased bleeding in hemophiliacs.

**Potential drug interactions:** Do not take with proton pump inhibitors (long-acting medicine for acid reflux): Prilosec-OTC, Prevacid, Aciphex or Nexium. May be taken 12 hours apart from short-acting acid reflux medications (H2 inhibitors or blockers) like Zantac and Axid. Antacids like Mylanta must be taken at least two hours apart from Reyataz. Must be taken an hour apart from Videx, due to Videx's buffer. Boost with Norvir (300 mg Reyataz with 100 mg Norvir) when taking in combination with Sustiva. With Fortovase, use six Fortovase capsules with 400 mg Reyataz once-a-day with a high-fat meal (further efficacy and safety information is needed).

Viread decreases the concentration levels of Reyataz. In addition, Reyataz increases Viread concentrations. The reasons for these interactions are not fully understood. Higher Viread concentrations could increase Viread -associated adverse events, including renal disorders. The FDA suggests that patients receiving Reyataz and Viread should be monitored for Viread-associated adverse events. When coadministered with Viread, it is recommended that Reyataz 300 mg is given with Norvir 100 mg and Viread 300 mg (all as a single daily dose with food). Reyataz without Norvir should not be taken with Viread.

Do not take with Tambocor, Rythmol, Versed, Halcion, Hismanol, Seldane, rifampin, ergot derivatives (such as Cafergot, Wigraine and Methergine, D.H.E. 45, in any form—serious interactions seen with dilation during gynecological exams), garlic supplements, and the herb St. John's wort. Reduce dose and frequency of rifabutin to 150 mg once-a-day. Do not use Zocor (simvastatin) or Mevacor (lovastatin); lipid-lowering alternatives are Lipitor (atorvastatin), Lescol, and Pravachol (pravastatin), but they should be used with caution due to potential for liver toxicity.

Protease inhibitors increase blood levels of Viagra (sildenafil citrate), Cialis (tadalafil) and Levitra (vardenafil). Use with caution. Initially the Viagra dose should be 12.5 mg (½ of 25 mg tablet) and increased as needed and tolerated. It's recommended that people on PIs do not exceed 25 mg of Viagra in a 48-hour period because of potential for serious reaction. Use Cialis at reduced doses of 10 mg every 72 hours and Levitra at reduced doses of no more than 2.5 mg every 72 hours, with increased monitoring for adverse events.

**Tips:** Not recommended for people with previous PI treatment failure. Unconjugated bilirubin is not associated with either disease or liver toxicity, the usual cause of jaundice. Needs an acidic environment, which you get from taking it with food. Study is underway to see if a Videx dose adjustment is needed. Reyataz, approved in June 2003, is the second-newest protease inhibitor on the market. Reyataz is the only protease inhibitor shown to lead to the 150L mutation in HIV. This indicates a lack of cross-resistance to other protease inhibitors. The manufacturer does not recommend that it be taken with Crixivan because of the increased potential for jaundice.

### Doctor

Reyataz is the newest PI, having been approved for use in 2003. Its main advantage is its convenience. Although it can be prescribed as two pills once a day, many practitioners prefer to boost it with Norvir. Recent studies suggest that boosted Reyataz is equal in potency to Kaletra. Boosted or unboosted, Reyataz has minimal impact on lipid levels and is well tolerated. Its major side effect is jaundice, characterized by a yellowing of the eyes and, to a lesser degree, the skin due not to liver disease but to the harmless impairment of bilirubin clearance. The jaundice resolves when Reyataz is stopped; it also may become less marked with the passage of time. Viread can lower Reyataz blood levels; in this setting, Reyataz should be boosted with Norvir. —Ross Slotten, MD

### Activist

Waiting for atazanavir to emerge from the pipeline in 2003, I thought: a potent once daily PI (two puny capsules) with little impact on lipids and no gut disturbance? Bring it on! Oh, wait. Did I say potent? It was approved for use as a single PI in a regimen but it makes some people nervous without a ritonavir boost—especially if it's not their first regimen or they've got a high viral load, or if they want to use it with Viread or efavirenz (which reduce its levels). Atazanavir can raise bilirubin levels for some people, to the point of appearing jaundiced. Turning yellow ain't cool, for sure, but there doesn't appear to be any liver injury associated with it and it resolves when you stop the drug. Atazanavir's big drag: if you have acid reflux, the best atazanavir will let you do is short-acting medications. No proton pump inhibitors allowed. —Heidi M. Nass

## Two 700 mg tablets + 200 mg Norvir once daily

**Class:** HIV protease inhibitor (PI)

**Standard dose:** Once-a-day—two 700 mg tablets with two 100 mg Norvir. Twice-a-day: either two 700 mg tablets (without Norvir) or one 700 mg tablet with 100 mg Norvir twice daily. PI-experienced patients should use Lexiva twice daily with Norvir. No food restrictions (may be taken with or without food) with any dosing. Take missed dose as soon as possible, but do not double up on your next dose.

**AWP:** $629.40 / month

**Manufacturer contact:** GlaxoSmithKline, www.lexiva.com, 1 (888) 825–5249

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** The most common side effects include: nausea, rash, diarrhea, headache, vomiting, fatigue, mood disorders, abdominal pain, and mouth numbness. Rash occurred in about 19% of patients, but severe rashes were uncommon. If you experience a rash, notify your doctor. For mild or moderate rashes, your doctor may choose to continue Lexiva, with close follow-up and monitoring. Because Lexiva is a sulfonamide, it should be used with caution in patients with allergies to sulfa drugs. Side effects and laboratory abnormalities were similar when Lexiva was taken once or twice daily, with or without Norvir.

As seen with all other protease inhibitors are increased levels of cholesterol and triglycerides, except possibly unboosted Reyataz (atazanavir) and these increased levels may be associated with heart disease. Side effects and laboratory abnormalities were similar when Lexiva was taken once of twice daily, with or without Norvir. Other possible side effects are lipodystrophy (body fat changes, including thinning of the face, arms and legs, with or without fat accumulation in the stomach, breasts and sometimes the upper back), onset of new cases or worsening of diabetes (see your doctor promptly) and increased bleeding in hemophiliacs.

**Potential drug interactions:** Not recommended to be taken with Kaletra. When taken with Sustiva, boost a once-daily dose of Lexiva with 300 mg of Norvir. There is insufficent data on combining Lexiva, Kaletra and Sustiva—consider using Therapeutic Drug Monitoring (TDM). Like all PIs, do not take with Tambocor (flecainide), Rythmol (propafenone), Versed, Halcion, Hismanol, Seldane, rifampin, ergot derivatives (such as Cafergot, Wigraine and Methergine, D.H.E. 45, in any form—serious interactions seen with dilation during gynecological exams), and the herbal supplement St. John's wort. Do not use Zocor (simvastatin) or Mevacor (lovastatin); lipid-lowering alternatives are Lipitor (atorvastatin), Lescol, and Pravachol (pravastatin), but they should be used with caution due to potential for liver toxicity. Oral solution contains alcohol, so do not use with Antabuse or Flagyl. Also avoid dihydropuridine calcium channel blockers.

Protease inhibitors increase blood levels of Viagra (sidenafil citrate), Cialis (tadalafil) and Levitra (vardenafil). Use with caution. Initially the Viagra dose should be 12.5 mg (½ of 25 mg tablet) and increased as needed and tolerated. It's recommended that people on PIs do not exceed 25 mg of Viagra in a 48-hour period because of potential for serious reaction. Use Cialis at reduced doses of 10 mg every 72 hours and Levitra at reduced doses of no more than 2.5 mg every 72 hours, with increased monitoring for adverse events.

**Tips:** Studies have demonstrated that protease inhibitor-experienced patients should take Lexiva 700 mg with Norvir 100 mg, both twice daily. The once daily dosing is not recommended for treatment-experienced patients for whom a PI therapy has previously failed. It is important to take Lexiva exactly as your doctor instructs, and not to change dosing without discussing with your doctor. The FDA points out that the study comparing Lexiva/Norvir against Kaletra in protease inhibitor experienced patients was not large enough to show that the combination was clinically equivalent to Kaletra.

Lexiva is a "pro-drug" formulation of Agenerase. This means that when you take this pill, your body converts it to Agenerase. 700 mg of Lexiva is roughly equivalent to 600 mg of Agenerase. This new formulation is an improvement because it helps to make the pills smaller and easier to swallow. The new formulation also allows the drug to be given with fewer number of pills per day (4 per day).

### Doctor

Lexiva, or fos-amprenavir, is one of the newer PI s, though it is actually a form of amprenavir, or Agenerase. The advantage of Lexiva over its relative is that it can be taken in much smaller quantities: when given unboosted, Agenerase is a mouthful, like unboosted Fortovase. Lexiva can be given unboosted, two pills twice daily; however, most practitioners prefer to boost it with Norvir—one Lexiva plus one Norvir twice daily. Lexiva has a slightly different resistance pattern than some of the other PI s; but like most HIV meds, it's most effective as a first-line agent, rather than as part of a salvage regimen. It's hard to see Lexiva's advantage over Kaletra and boosted Reyataz, though it's certainly as effective as its competitors. As usual with PI s, diarrhea is the most common side effect.—Ross Slotten, MD

### Activist

Maybe it wouldn't win the Extreme Drug Makeover contest, but Lexiva would be the likeliest entry from the HIV division. This new, pro-drug version of amprenavir gets converted into the old version, Agenerase, once it gets inside the body. Getting there, though, requires many fewer pills and has less gut distress and rash. In clinical trials, fosAmprenavir caused less diarrhea than nelfinavir—which is a little like saying I'm less conservative than George Bush (who isn't?)—but it performed better, too. It also did okay against Kaletra in people on their second or third PI regimen. Lexiva can be dosed with or without a ritonavir boost, and once or twice daily, all depending on whether you've taken protease inhibitors before or not. It has drug interactions of the PI variety and cannot be used with Kaletra. If you are allergic to sulfa drugs, proceed with caution. —Heidi M. Nass

**Brand Name:** Not yet established

**Common Name:** tipranavir

Photo not available due to experimental status

**Class:** experimental protease inhibitor

**Standard dose:** Dose not yet established because of experimental drug status, but studies are proceeding with a dose of two 250 mg capsules with two 100 mg capsules of Norvir, both twice daily. It will likely be dosed with food.

**Manufacturer contact:** Boehringer-Ingelheim, www.boehringer-ingelheim.com

**AIDS Clinical Trials Information Service:** 1 (800) TRIALS–A (874–2572)

**Potential side effects and toxicity:** Mostly gastrointestinal-related: mild diarrhea, nausea, vomiting and fatigue. In clinical trials symptoms have been managed by having a light snack with the drug. Other side effects include headaches, dry mouth and dizziness. This dose of tipranavir was fairly well tolerated in Phase II studies, with few patients needing to discontinue this combination due to side effects, but full side effect profile isn't usually determined until drugs move into Phase III. See Norvir for more details on potential side effects.

**Potential drug interactions:** Not yet finalized. Should not be given with other protease inhibitors because it greatly lowers their blood levels due to its mechanism of action (a reduction of 55% for Kaletra, 56% for Agenerase and 81% for Fortovase—expected to lower other PI levels as well). This drug is metabolized by the liver (same as most of the other protease inhibitors). It must be dosed with Norvir. No dose adjustments are likely to be necessary when given with Videx, Viread or Sustiva. See Norvir for the drug interactions possible.

**Tips:** Tipranavir is different from the other protease inhibitors currently approved. Its difference is how the drug is built. It's the first in a new class (third generation) of protease inhibitors called non-peptidic protease inhibitors. Initial studies indicate that tipranavir may be active against strains of HIV that are already resistant to currently available peptidic protease inhibitors. As resistance becomes more and more an issue for treatment-experienced individuals, this type of drug offers hope.

The results furthest out in people are still preliminary, six months data from two studies called RESIST 1 and RESIST 2. In both studies, taking tipranavir at least doubled the odds of doing well. Adding Fuzeon to tipranavir further increased those odds. (This shows that—as usual for treatment-experienced people—you might really need another "new" drug to have the best chance of success with tipranavir.) It is important to note that the people in these studies had taken extensive HIV therapy before, including all of the first three classes of HIV drugs on the market and at least two protease inhibitors. It is difficult to significantly decrease viral load in a group like this. RESIST-1 enrolled 620 patients and RESIST-2 enrolled 863 patients. The large numbers enrolled were necessary to make sure the drug worked in these populations.

All people were taking an "optimized background." This means that they were using a regimen that was expected to have the most success for them according to resistance test results. (These trials used genotype resistance testing.) The studies compared the people taking Norvir-boosted tipranavir to those taking a different protease inhibitor combination (Kaletra, Agenerase or Fortovase). In RESIST 1 the number of people going below 400 viral load was 34.7% (47% with Fuzeon) vs. 16.5% (21.9% with Fuzeon). Just looking at the people with one (or greater) log drop in their viral load—a significant decrease—the results were 41.5% for the entire tipranavir group vs. 22.3% for the group taking other PIs. In RESIST 2, the number of people on tipranavir going below 400 viral load was 33.6% (38.5% with Fuzeon) vs. 13.1% (13% with Fuzeon). Looking at one (or greater) log drop, results were 41% for the tipranavir group vs. 14.9% of the other group. T-cell increase was 31 vs. 1.

Tipranavir is expected to do less well for people with combinations of certain protease-related mutations. It's all still being figured out. Although tipranavir has to be taken with 200 mg twice daily of Norvir, it actually lowers the blood levels of Norvir. So, you may not see as much of the gastrointestinal side effects as you might expect. *—Reviewed by Patrick G. Clay, Pharm.D.*

To learn about getting free tipranavir, call the Expanded Access Program at 1–888–524–8675 or visit www.tpv-eap.com. In private phone calls, Abbott reps promised higher booster dose free to people using it, but there's no official word as of yet.

## Doctor

Tipranavir is a new protease inhibitor whose structure is somewhat different from current protease inhibitors. Its manufacturer, Boehringer-Ingleheim, hopes that it will be active against virus resistant to other PIs, though it is far from certain that this will be the case. Tipranivir is currently in Phase III trials, which means it probably will not be generally available until at least 2006. A small number of people will be able to obtain the drug through an expanded access program in 2005. To increase its potency, tipranivir must be combined with Norvir at 200 mg twice daily, which might not be good news for those people who can't tolerate Norvir.—Ross Slotten, MD

## Activist

Waiting on tipranavir's release feels like watching the proverbial pot that refuses to boil. This feeling is exacerbated, no doubt, by the pressing need for good agents that work on resistant virus, and the trickle of new drugs we see in our foreseeable future that might meet this need. In the first big trial of tipranavir (with a ritonavir boost—the way it will come to market) in people with multiple PI experience, it did a better job than other boosted PIs at dropping viral load and raising CD-4 cells. However, it raised lipids and liver enzymes more, too. Note that tipranavir uses more ritonavir than other boosted PIs, and more ritonavir = more gut distress. The study did not include people with profound PI resistance and results are only available for the first 24 weeks. We'll have to stay tuned to see how this PI will serve the ever growing number of people in our community whose viral resistance is broad and deep. —Heidi M. Nass

## One 90 mg subcutaneous injection twice daily

**Class:** fusion inhibitor

**Standard dose:** One subcutaneous (under the skin) injection of 90 mg (1 ml) twice daily into the upper arm, thigh or abdomen. No food restrictions (take with or without food). Take missed dose as soon as possible, but do not double up on next dose.

**AWP:** $2,152.21 / month for 90 mg kit

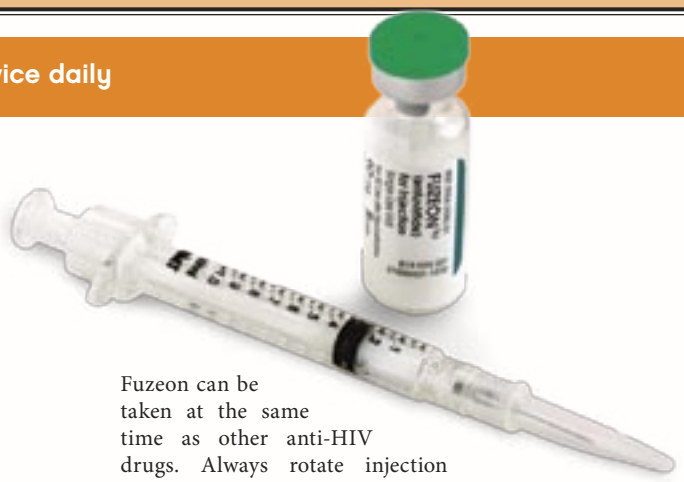
**Manufacturer contact:** Roche Pharmaceuticals and Trimeris, www.rocheusa.com, www.trimeris.com, www.fuzeon.com, 1 (877) 4–FUZEON (438–9366)

**AIDS Treatment Information Service:** 1 (800) HIV–0440 (448–0440)

**Potential side effects and toxicity:** The most common are Injection Site Reactions (ISRs), which occur in virtually all patients. The severity of reactions is variable, and for most is mild to moderate. Symptoms could include itching, swelling, redness, pain or tenderness, hardened skin or bumps; others include headache and fever. Bumps termed "nodules" seem to occur more frequently and severely in areas of high muscle mass (most notably the center of the stomach—the abs—and the legs). They will hurt with movement. Allergic reactions are possible. In studies, pneumonia happened more often in the patients on Fuzeon. It is unclear if this was related to the use of Fuzeon. Report cough, fever or trouble breathing to your healthcare provider right away.

**Potential drug interactions:** To date none that require dose adjustment have been reported.

**Tips:** To minimize injection site reactions, inject where you can pinch an inch. If not, then be sure to use half the length of the needle. Inject slowly and apply a gentle massage after injection. Try using vibrating devices after injections. Careful reconstitution of drug is also helpful. The drug must be carefully reconstituted for 30–45 minutes (for the two daily doses—refrigerate the dose—after reconstitution—that will be taken later, and then allow it to warm to room temperature before using). Never shake—it will foam. Follow instructions to avoid infection. ISR may worsen when injection is repeated in the same spot or given deeper than intended for example, into the muscle.



Fuzeon can be taken at the same time as other anti-HIV drugs. Always rotate injection sites frequently. Never inject into moles, scars, bruises, nodules or the navel. Research is needed in alternate site subcutaneous areas, such as the buttocks or the upper back.

Fuzeon is the first in a new class of anti-HIV compounds called fusion inhibitors. Fusion inhibitors block fusion of HIV with host cells before the virus enters the cell and begins its replication process. Because of injections, this drug will most likely be used in the heavily-treatment experienced and salvage therapy options. However, because the drug is so good, it should be studied (and used more) in people with earlier disease or those on their second or third regimen. Two large Phase III studies showed good viral load decrease when added to an optimized antiviral combination in heavily treatment-experienced people, including those with protease inhibitor-resistant virus and those who've taken all three current drug classes. Participants used 3 to 5 antivirals in addition to Fuzeon and both genotype and phenotype tests.

### Doctor

Fuzeon is a novel anti-HIV drug, the first in the class known as fusion inhibitors. If it were not administered as an injection, it no doubt would be a first-line therapy, because of its tolerability and potency. Currently, it is prescribed in salvage therapies, though it works best if it can be paired with another agent that the patient is not resistant to. —Ross Slotten, MD

### Activist

When the first T-20 data came out, the graphs showed how much better it performed with one, preferably two, new agents than as the only new agent in a regimen. It seemed like a moot point to me: people with two new agents available wouldn't likely opt for a drug that costs a mint, is injected twice daily, leaves big lumps behind and isn't that durable…would they? Well, maybe they should—it appears T-20 may do better the earlier it's started. In my circle, a ritual has emerged when someone starts T-20: we ooh and aah at the initial viral load drop (many people taking the drug haven't seen their numbers so low in years), followed by deep sighs some weeks or months later when the viral load breaks through and starts to climb. There's a lot of hope—and lives—pinned on T-20 and tipranavir for people with multi-drug resistance. —Heidi M. Nass

# A New Era in HIV Treatment: The Entry Inhibitors

*by Daniel S. Berger, MD*

*Editor's note: In the previous issue of Positively Aware, the November/December 2004 "The Buzz—New Once-a-Day Drugs: Truvada and Epzicom" was edited down due to space and time constraints. Please visit http://www.tpan.com/publications/positively_aware/nov_dec_04/buzz.html to view the original, unedited version of the article.*

HIV treatment as we know it is poised to undergo a seismic shift. New long-awaited "Star Wars" drugs are on the brink of becoming part of our arsenal; they belong to the new class called entry inhibitors. While older antivirals are effective because they inhibit viral replication after the virus penetrates the CD4 T cell, several new agents in development, blocking HIV from getting into the cell from the get-go, are making their presence known at select institutions participating in specific studies. These entry inhibitors stop the virus from entering the T cell by binding to a co-receptor; a resultant distortion of that receptor binding-site blocks HIV entry. This is a very exciting time in treatment research; one can't help feeling revved up while conducting the studies at Northstar in Chicago.

The new entry inhibitors are being developed to fill specific unmet treatment needs. Existent mutations that foster resistance to antiviral therapy and combined residual virus replication have had a major negative impact on future options for patients. Additionally, constructing regimens with low pill burdens is paramount.

Previously, Fuzeon was the first drug to have an effect on the virus prior to its penetration into the cell; it blocks viral fusion, a step following the stage of viral co-receptor binding (figure 1). Fuzeon needs to be administered by the patient in two daily injections. In contrast, the new entry compounds are in pill form (thankfully) that will either be taken once or twice daily. There are actually two main steps that the virus needs to pass before it gets to the fusion stage. One of these steps is the co-receptor binding. This article will focus on the specifics and the CCR5 entry inhibitor.

### Understanding the mechanism of HIV entry

To understand entry inhibitors, one should have some basic knowledge of the mechanism of viral entry. The virus needs to pass through several hoops before it finds itself within a (CD4+) T-cell (see Figure 1). First, the virus must bind to the CD4 component of the T-cell. Specifically, one of the envelope proteins of the virus, the gp120, binds directly to this CD4 receptor on the T-cell surface.

This induces a confirmational change or change in the shape of the outer portion of the cell, which now allows for the next step, co-receptor binding. In this step, the virus uses one of two possible receptors: CCR5 and/or CXCR4, which is on the T-cell itself.

The virus' preference for using one co-receptor versus another is referred to as "viral tropism." Most individuals' virus uses the CCR5 co-receptor (and is called CCR5 tropic virus). Many fewer patients use the CXCR4. Some individuals harbor virus that uses both types of receptors. Receptor binding eventually allows for the fusion step to take place and subsequent viral penetration into the cell. The CCR5 inhibitor's effect in blocking the co-receptor binding step does so by causing another confirmation change—it distorts the shape of the receptor site, thus blocking further steps for entry.

The fusion step is the site of activity for T-20 (Fuzeon). Once inside the cell, other targeted sites can block HIV replication, hence the nukes, non-nukes and protease inhibitors. Different from these older antivirals, the CCR5 entry inhibitors target human cells themselves, since the co-receptor is on the surface of human T-cells.

### Tropism

Both CCR5 and CXCR4 are made up of transmembrane proteins. As stated above, the viral preference for using a particular type of receptor is referred to as "tropism". Tropism can be analogous to a description of the virus' preference to enter the T-cell through a particular door and which door it uses—whether it is CCR5 or CXCR4. Tropism plays an important role in prognosis and can lead to consequences in patient response to a particular entry inhibitor treatment.

What factors affect the virus choice for the particular co-receptor is presently unknown.

To make matters more complicated, if you suppress the virus' ability to get into the cell by blocking this CCR5 doorway, theoretically the virus can then select or choose to use the CXCR4 door. In this scenario, the virus population is referred to as switching its tropism to CXCR4.

Also, in patients who have not been on HIV therapy, who harbor the viral tropism for CXCR4, often switch to CCR5 tropism after successful treatment.

Finally, some virus is "dual tropic," meaning their HIV can use both co-receptors to fuse onto the cell. And some patients have two virus populations for which some virus utilizes CCR5 and some of their virus

uses CXCR4; these individuals manifest "mixed tropism."

Specific drugs targeting the binding at the CCR5 co-receptor are not effective in individuals who harbor CXCR4 exclusively. Fortunately, the CCR5 co-receptor is used by the great majority of HIV strains and the majority of HIV-positive individuals. Also, most patients during early infection, being healthier, more commonly use the CCR5 co-receptor.

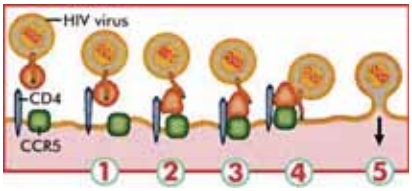
People with more advanced stage HIV/AIDS—patients with lower T-cell counts and higher viral load, are at increased likelihood of having CXCR4 tropism. However, there is still a high prevalence of CCR5 tropism among those with low T-cells or advanced disease. Other predictors of viral tropism also include length of time on antiviral treatment. It is expected that individuals who have primarily CCR5 tropism will respond to this new class of drugs. For patients with mixed or dual tropism, CCR5 inhibitor treatment effect is yet unknown, but is also being studied.

### Studying the effect of entry inhibitors

Several years ago, a study was performed in patients receiving Schering's SCH-C, the first CCR5 inhibitor. This work was the first proof of the principle that blocking viral entry at the CCR5 co-receptor site can be very effective treatment. Though treatment successfully demonstrated potent antiviral activity, during the pilot study, a cardiac abnormality was observed to occur as a side effect. Thus Schering has decided to study their second candidate compound instead, SCH-D. Trials with SCH-D finally began earlier this year. Other drugs being studied in this class include Glaxo's GW873140 (140) and Pfizer's UK-427.

A Phase I study with GW873140, or "140" for short, was presented in October at the 44th ICAAC in Washington, D.C. In this study, 40 participants were given four different doses of "140" either once or twice daily for 10 days. This initial trial was undertaken in patients who were either treatment naïve (never treated) or treatment experienced, but none of the patients in this small group were taking other antiviral therapy during this period. Also the patients had to have CCR5 tropic virus, demonstrated by the PhenoSense assay (blood test for tropism) developed by Virologic (see below). The results showed potent antiviral effect; a greater suppression of HIV (viral load decreases) was observed with the highest doses (1.66 log drop). Also important, the CCR5 receptor remained occupied or blocked for several days after stopping the drug.

*Fig.1 - T cell*




*Steps comprising viral entry: New drugs are being developed to block various steps in viral entry.*

*1. CD4 binding*

*2. Conformational change*

*3. CCR5 and/or CXCR4 co-receptor binding*

*4. Membrane insertion*

*5. Fusion*

Side effects observed during the study were mainly mild degrees of gastrointestinal symptoms. They occurred during the very start of treatment as either soft stool, nausea or mild abdominal pain, most of which disappeared or resolved within one to three days, while continuing the treatment. None of the patients needed to discontinue the study because of side effects.

### Phase II trials

In CCR5 studies, all patients are required to be tested for co-receptor tropism; HIV-positive individuals are being screened to find out which virus they harbor (CCR5, CXCR4, mixed, or dual tropism). This test is done by taking a patient's blood sample and performing the assay created by Virologic, a company well known for their extensive work on viral resistance testing (including Phenosense GT) and their replicative capacity test that is often helpful in making treatment decisions. The test does not distinguish between dual or mixed tropism.

Northstar in Chicago is participating in a 96-week study for which patients are receiving Kaletra in combination with various doses of "140." Kaletra was chosen for several reasons, including its favorable pharmacokinetics (drug metabolism and length of time in blood), and its low barrier for resistance. Additionally, Kaletra boosts the blood levels of 140. An earlier study done by GSK found "140" levels boosted by more than 7-fold in the presence of Kaletra. Potentially, other boosted protease inhibitors can be used with "140" and likely provide for less frequent dosing (once daily). (In its own right, a recent small study by Dr. Joseph Gathe showed the use of Kaletra as monotherapy to be effective.)

During this Phase II study, one expects to learn more regarding the drug's antiviral effect and the further use of this new class of treatment. Viral tropism and data on patients co-infected with hepatitis C will also be collected. While drug levels of Kaletra are not affected by "140," more about the interaction of the two drugs will also be gathered. We anticipate this work will be very influential on future HIV treatment and will provide an abundance of information about entry inhibitors.

### Conclusion

As we look forward to the promising benefits of CCR5 inhibitors and drugs that affect viral entry, it is remarkable to reflect back on the incredible progress being made with every passing year. We are clearly living in a Star Wars era. This new class of drugs may turn out to be a knockout that will have great influence on the course of HIV treatment and ultimately affect the treatment landscape.

Drugs such as "140" have demonstrated potent activity in their own right during pilot studies. During this next phase of research "140" is pitted together with another agent such as a boosted protease inhibitor with a high genetic barrier; and this has the potential to exhibit the most potent HIV treatment to date. One antiviral will be effective on the outside preventing viral entry, while the other drug shuts down replication within the cell.

While there are some uncertainties regarding this new class of drugs, including what happens to envelope tropism among subjects who may fail with CCR5, or what effect these drugs will have on mixed tropism, we are primed and ready for the challenges and experiences ahead.

*Daniel S. Berger, MD, is Medical Director of Chicago's largest private HIV treatment and research center, NorthStar Healthcare and Clinical Assistant Professor of Medicine at the University of Illinois at Chicago. He serves as medical consultant for* Positively Aware *and serves on the HIV Medical Issues Committee for the Illinois AIDS Drug Assistance Program, the Board of Directors for the AIDS Foundation of Chicago and the Editorial Board of Contagion: Reports, Cases, and Commentaries in HIV and Infectious Disease Research. Dr. Berger can be reached at DSBergerMD@aol.com or (773) 296-2400.*


# 2004 Index of Positively Aware

*compiled by Keith Green*

# TPAN Events Calendar

**All events held at TPAN unless otherwise indicated.**
**For additional information on these events please contact TPAN at (773) 989-9400.**

## January 2005

| Date | Time | Event |
|---|---|---|
| Wednesday 5th | 7:30 pm | Committed to Living: HIV Medication Review |
| Monday 17th | All Day | Office closed in observance of Martin Luther King, Jr. Day |
| Thursday 20th | Evening | Committed to Living South: The Big 3—Diabetes, Blood Pressure and Cardiovascular Disease; Location TBD. With Dana Williams, St. Louis Community Wellness Project. Call (773) 989-9400 for more information. |
| Wed 26th - Fri. 28th | 9am–5pm | TEAM |

## February 2005

| Date | Time | Event |
|---|---|---|
| Wednesday 2nd | 7:30 pm | Committed to Living, Topic TBA |
| Thursday 10th | 6–10 pm | The Connection – an HIV "Dating Game". Ann Sather restaurant 6-8 pm, Berlin nightclub 8-10 pm. Supported by Gilead and APositiveOutlook.com |
| Wednesday 16th | 6–9 pm | TEAM update |

# Programs and Meetings

**All meetings held at TPAN unless otherwise indicated:**
**5537 North Broadway, Chicago.**
**Office hours: Monday–Thursday, 9 am–8 pm. Friday, 9 am–5 pm**
**phone: (773) 989-9400 • fax: (773) 989-9494**
**e-mail: programs@tpan.com • www.tpan.com**

**Support groups sponsored by the Chicago Department of Public Health**
**Peer Support and Buddy programs sponsored by the AIDS Foundation of Chicago**

## Monday

### Medical Clinic

HIV/Syphilis/Hepatitis C testing and full medical care for HIV-positive clients is available. Program is offered by Access Community Health Network. Call for an appointment. From 10 am–6 pm.

### TPAN Daytimers

A support group for people with HIV who prefer to meet during the day. Meets from 10:30 am–12:30 pm.

### Reiki

Energetic healing practice that utilizes hands-on touch and focused visualization. Monday by appointment only.

### HEALTH

Support group for people co-infected with HIV and hepatitis. Meets from 7-9 pm.

### Couples Group

Support group for couples affected by HIV. One or both partners may be HIV-positive. Meets 7:30–9 pm.

### Crystal Meth Anonymous (CMA)

Support group for individuals for whom crystal meth has become a problem. Meets 7:30–9 pm.

### Spirit Alive!

A collaborative effort of AIDS Pastoral Care Network (APCN) and TPAN. Meets from 7:30–9 pm. Socials every other month, on 3rd Monday beginning in November.

## Tuesday

### Medical Clinic

See description on Monday. Call for an appointment. From 9 am–12 pm.

### Yoga

All levels of yoga are welcome. Meets from 10–11 am.

### Positive Progress

A peer-led group for HIV-positive individuals in recovery. Meets from 7–9 pm.

### Living Positive

HIV-positive individuals discuss how being positive affects life and relationships. Socials and speakers on occasion. Meets from 7:30–9 pm.

## Wednesday

### Reiki

See description on Monday. Wednesday by appointment only.

### Test Aware

TPAN's new rapid HIV counseling and testing program. Learn results in around 20 minutes. Wednesday 10 am-4 pm. or by appointment.

### Needle Exchange Program

Through a collaborative effort of Chicago Recovery Alliance and TPAN, a free, anonymous, legal syringe exchange and HIV/AIDS prevention are offered Wednesdays from 5–7 pm, or by appointment.

### Poz Leathermen

Support and social group for HIV-positive leathermen and friends. Meets from 7:30–9 pm.

### SHE (Strong, Healthy and Empowered)

HIV-positive women discuss needs, concerns and issues facing women with HIV. Meets from 7:30–9 pm. Socials every 4th Wednesday.

## Thursday

### Yoga

All levels of yoga are welcome. Meets from 10–11 am.

### Medical Clinic

See description on Monday. Call for an appointment. From 12 pm–8 pm.

### TPAN Daytimers

See description on Monday. Meets from 10:30 am–12:30 pm.

### Needle Exchange Program

See description on Wednesday. From 2–5 pm, or by appointment.

### BUS (Brothers United in Support)

Support group for HIV-positive gay and bisexual men of African descent. Monthly socials and speakers on occasion. Meets from 7–9 pm.

### Positive Now

Support group for newly diagnosed HIV-positive individuals who seek support, education and the opportunity to share their experiences in a relaxing, empowering environment. Meets from 7–9 pm.

### Pulse at Berlin

A weekly social for HIV-positive individuals and friends. Meets from 6–10 pm at Berlin Nightclub, 954 W. Belmont, Chicago.

## Friday

### Needle Exchange Program

See description on Wednesday. From 2–5 pm, or by appointment.

## Scheduled By Appointment

### FASN (Family AIDS Support Network)

A group for family, friends and caregivers. Call Betty Stern at (773) 989-9490.

### Individual Counseling

AIDS Pastoral Care Network (APCN) professionals provide individuals with one-on-one counseling on Mondays. Ask for Sherry or Betsy at (708) 681-6327.

### Peer Support Network/Buddy Program

Trained volunteers provide one-on-one peer, emotional support to individuals living with HIV. Call Barb at (773) 989-9400.

### Speakers Bureau

Individuals are available to community groups to educate peers on HIV, safer sex, and harm reduction. Call Matt at (773) 989-9400.

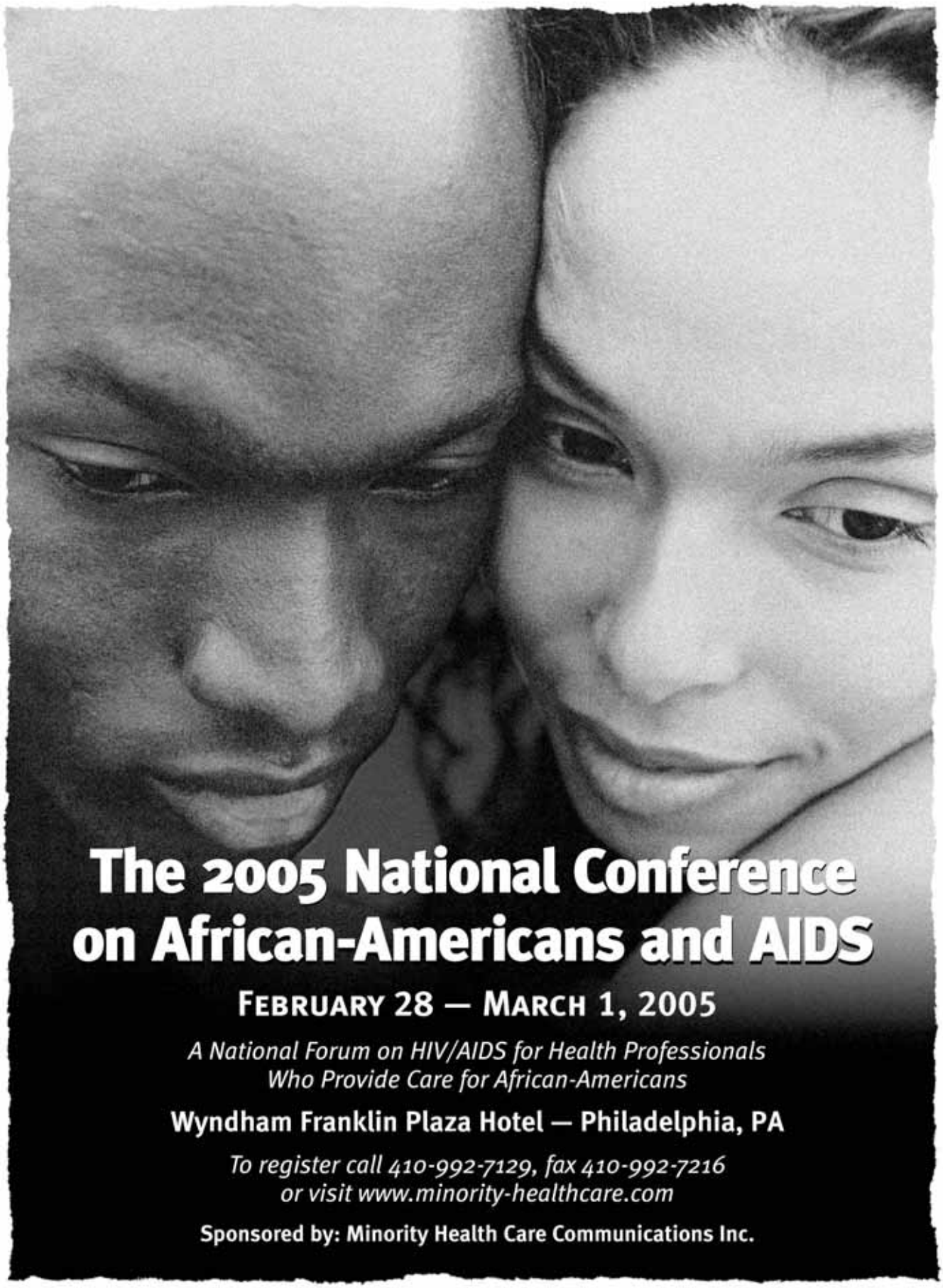
### TEAM (Treatment, Education, Advocacy and Management)

Peer-led program integrating secondary prevention and treatment education to provide individuals the training and knowledge to more successfully support other individuals impacted by HIV. Call Montré at (773) 989-9400.

## Miscellaneous

### livingpos18to24@aol.com

An AOL chat room for young adults (ages 18–24) who are HIV-positive. Monday through Friday from 3–5 pm. Contact email livingpos18to24@aol.com


The 2005 National Conference on African-Americans and AIDS
February 28 — March 1, 2005
A National Forum on HIV/AIDS for Health Professionals Who Provide Care for African-Americans
Wyndham Franklin Plaza Hotel — Philadelphia, PA
To register call 410-992-7129, fax 410-992-7216 or visit www.minority-healthcare.com
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design: Kevin Putz, Toolbox Inc. www.toolboxinc.com