When To Start: A Debate

With new information coming in from various studies, is it time to revise the guidelines on when people with HIV should start treatment?

by Mark Milano

The U.S. Department of Health and Human Services guidelines are continuously evolving. They have always recommended treatment for anyone with a CD4 count below 200. But recommendations have changed over the years for people with higher CD4 counts. Throughout the 1990s, they recommended that “treatment should be offered” to anyone with a CD4 count below 500 or a viral load above 20,000.

In 2001, the guidelines were revised to say that “treatment should generally be offered” to people with a CD4 count between 200 and 350, “though controversy exists.” For people above 350 with a viral load above 55,000, “some experts would recommend starting therapy... some would defer.” For those above 350 but with a viral load below 55,000 “many experts would defer therapy and observe.”

In 2004, the “controversy” about people between 200 and 350 was dropped: “Treatment should be offered following full discussion of pros and cons with each patient.” For those with a CD4 count above 350, the viral load threshold was raised: with a viral load above 100,000, “most clinicians recommend deferring therapy, but some...will treat.” If below 100,000, “defer therapy.”

The current guidelines, adopted in 2007, simply state that “antiretroviral therapy should be initiated” in anyone with a CD4 count below 350. For people above 350, “the optimal time to initiate therapy... is not well defined.”

The definitive answer to this question will hopefully come from the START study, which has just begun. It will even-continued on page 3
LETTERS TO THE EDITOR

To The Editor:

I work for the Interagency Coalition on AIDS and Development (ICAD), a non-profit membership organization. We are holding our AGM and Workshop in September, 2009, focusing on HIV prevention in the African and Caribbean Diaspora.

We recently received your Spring 2009 issue which focused on HIV in communities of color, and found it very relevant to our workshop. I plan to make it available to workshop participants. It was particularly relevant to our work at ICAD, as addressing HIV within the African and Caribbean Diaspora has been a programmatic focus in recent years. This has been in response to the disproportionate number of Black people testing HIV positive and to the need identified by ICAD member ASOs challenged by how best to respond to the increasing number of Black people needing services.

Kate Alexander
ICAD

To the Editor:

I had the good fortune to obtain a copy of your Winter 2009 edition “Caring for Youth with HIV” and I was wondering if I could obtain copies for the staff here.

We are currently addressing the issues surrounding our adolescent and young adult population and this edition is excellent and much appreciated.

Once again, thank you for this great publication.

Regards,

Peter Oates RN, MSN, NP-C, ACRN
Manager, Health Care Services
François-Xavier Bagnoud Center,
School of Nursing at UMDNJ

You may have noticed that this issue of Achieve comes to you on glossy paper that makes for a better reading experience. We’re happy to report that this improvement came without additional cost.

Achieve would love to hear from you! Please send your comments to: Letters to the Editor, Achieve, 230 W. 38th St., 17th floor, New York, NY 10018
Or email them to: achieve@acria.org

Pomegranate Juice
People who have not taken HIV meds for at least 90 days will drink pomegranate juice or placebo juice daily for 10 to 18 weeks to study its effect on the heart, quality of life, and HIV viral load.

Ibalizumab
People who have taken HIV drugs will receive infusions of ibalizumab (a monoclonal antibody designed to block HIV entry into CD4 cells) twice a month for 24 weeks or longer, along with other HIV drugs.

Crofelemer for Diarrhea
People 18 and older who have persistent diarrhea will take crofelemer (a new anti-diarrhea drug) or placebo tablets for 6 weeks. Then everyone will take crofelemer for 5 months.

Isentress in Pregnant Women
Pregnant women who are already taking Isentress will give several blood samples on two separate days in order to find the optimum dose of the drug during pregnancy. Compensation is provided.

Avandia and Serostim
People with insulin resistance will take Avandia or Serostim (growth hormone) or both for 6 months to see how they affect blood sugar, insulin levels, and body shape.

TAK-652
People who have taken HIV meds will take this new CCR5 inhibitor for 10 days with no other HIV meds.

Intelex
People who have taken HIV meds will take Intelex with Reyataz and an NRTI for 48 weeks.

For more information on these trials, contact us at 212-924-3934, ext. 121.
tually enroll 4,000 people with HIV who have CD4 counts above 500. Half of them will start HIV meds immediately and half will wait until their CD4 count drops below 350. A study like this should provide strong evidence on when to start treatment, since people will be randomly assigned to start or wait – unlike cohort studies in which they make that choice themselves.

But START will not report its first results until 2016. Should the guidelines be updated before then? Achieve asked ten experts their opinion on the long-standing “when to start” debate.

Do you think the current recommendation to begin HIV meds at a CD4 count of 350 should be changed?

**Gulick:** I think we should be starting treatment earlier. All the data seem to suggest the same thing. We don’t have data from a randomized study like START – the gold standard – but we do have cohort data from the ACCORD cohort suggesting a benefit to earlier treatment. They looked back at over 9,000 people in 22 different cohorts who had begun treatment at different levels – one was 350, one was 500 – and they found a clear survival benefit when people started earlier. So I would advocate to anybody that if you’re ready to go on treatment, you should start.

**Phair:** The data from ACCORD is observational only, and the implication is that somewhere between 350 and 500 would be an appropriate place to start. But until we have data from a randomized trial like START, I don’t think we have data to justify changing the guidelines. Even the newer HIV meds still have side effects.

**Nass:** More and more data are suggesting raising or even eliminating the CD4 threshold for starting treatment. ACCORD showed the dangers of uncontrolled HIV replication, even at higher CD4 counts. The data are hard to ignore and will likely only become more convincing.

**Huff:** Theoretically, I think treatment should begin when HIV is diagnosed. I think the next step will be to move the number to 500, though the evidence for doing that may not be strong.
survival benefit in people who started at higher CD4 counts. Clearly, treatment played a part in that, but were there other things that made those folks different? Were they more motivated? Was their living situation better? Were they not using drugs? I don’t think we need to wait for a randomized study like START to raise the recommendation, because there are enough data that say there’s a benefit.  

**Bookhardt-Murray:** I think there’s enough information out there that tells us we should really be considering starting earlier rather than later. Even up around 500 – I think the jury’s still out, but evidence points in that direction. It should always be weighed against toxicities and cost.  

**Horn:** I do think they need to be changed, to break the “cookie-cutter” approach. Yes, studies show that people with HIV have a higher risk of non-AIDS-related problems like heart disease and cancer even when their CD4 counts are above 350. But if you move the guidelines up to 500, you’re basically recommending treatment for everyone as soon as they enter care and I don’t know if that’s a good idea. It’s not all about the CD4 count – earlier treatment may be better for those with other risk factors like smoking or hepatitis C, to negate the added effects of uncontrolled HIV replication.  

**Emst:** The recommendation to wait until you reach 350 should be changed to read “for some patients.” We now have an amazing number of meds with fewer side effects and easier dosing. The benefits of earlier treatment that are appearing in the literature, coupled with the new meds, leads me to discuss earlier treatment with patients who don’t have adherence issues – earlier treatment is used more often than the guidelines recommend.  

**How important is this, since most people are diagnosed with CD4 counts below 350?**  

**Phair:** Right - the average in this country is around 190. The problem is that we are not diagnosing a third to a fourth of people until they are very immunosuppressed. The CDC has recommended testing people without going through all the hoops that we did in years past – to discuss the test, provide counseling once you make the diagnosis, and be sure the testing is tied to treatment access. So the question is very important, but I don’t think it affects the relevance of when people should start.  

**Gullick:** That’s old news and is likely to change as the CDC puts out the message that more people should be tested routinely. I think the numbers that people are quoting when they say that the average CD4 cell count at presentation is 200 are several years old and there are newer data to suggest that CD4 counts at diagnosis actually are going up. The average pregnant woman with HIV is diagnosed with a CD4 count in the 400s.  

**Huff:** It won’t mean a thing to the 25% of people newly diagnosed in New York City who already have AIDS. A serious campaign should be undertaken to increase community-based testing and diagnose people earlier. It would have the biggest bang for the buck, and it’s not being done.  

**Vail:** I think it’s still important because we’re moving to universal testing as a part of routine medical care. We’re going to see more people diagnosed with higher CD4 counts – we’re seeing that now. At our clinic, we have two populations: people who have been infected for 10 or 20 years with no T cells because they’ve been avoiding testing, and people coming in for routine STD testing who are being diagnosed with higher CD4 counts.  

**Nass:** I’m hopeful that moving recommendations to earlier treatment might push more providers to start testing people. People put the blame on written consent and no medicine is totally safe for everybody. These are really rough drugs when you think about it.  

**Gullick:** HIV is an infectious disease and we have good treatments that are relatively simple, nontoxic, and highly effective. So why are we even asking the question of when to start? People thought early on that this was a viral illness and you need to treat it – not only can you make the person better, you can probably reduce their chance of transmitting it to other people. It’s hard to name another infectious disease where we don’t start treating immediately. The treatments we had in the old days were complicated, toxic, and not very effective. Things have changed in the last 20 years.  

**Brown:** I don’t agree. That reminds me of the “hit hard, hit early, don’t let a single T cell die” approach, back when we were using Zerit and Crixivan. For someone with a normal CD4 count to be taking those meds would have been nuts. We were just looking at that one part of their lives – the amount of HIV in their body
– which matters a whole lot, but it’s still a whole life.

**Nass:** There are more and more data pointing to the damage of uncontrolled HIV replication and those data will likely only get more convincing. Knowing that suppressing the virus is desirable, perhaps for everyone, is not the same as saying everyone should be on treatment.

**Ernst:** I strongly disagree. I’d say they should be recommended to all patients after the risks and benefits are discussed, if there are no other problems like mental illnesses or addiction that would interfere with adherence.

**Vail:** In a perfect world, everyone with HIV would be on treatment in the same way that everyone with high blood pressure should be on treatment. But we don’t live in a perfect world. If we had a perfect pill that had no side effects and no risk of cross-resistance, it absolutely makes sense. But we don’t have that yet. At higher CD4 counts, will it do more harm than good?

**Jefferys:** From the perspective of the basic science, I understand this position better now than a few years ago. But from the perspective of real life, it still seems impractical and even undesirable, unless we can find a combination of meds that have zero impact on quality of life. I guess

**Would better HIV meds influence your opinion on when to start?**

**Brown:** They would, but we’re not going to see those changes quickly. One pill, once a day is certainly very convenient, but for someone who has never felt sick, who has never really seen people with advanced AIDS, particularly for a younger person, even that’s going to be too much for some. It may seem easy, but you have to take human nature into account. I hope we’ll eventually have meds that can be used like Depo-Provera, once a month, or an implant.

**Gulick:** I think the meds we have today, while not perfect, are very good. They fulfill all the qualities you would want in a medication that people have to take over the long term. It’s hard to get easier than one pill, once a day. The ACTG just formed a group to look at meds that would be less frequent than once a day. Different people want different things. Some people would like a patch or injection, others would not. Having several options would be nice. We used to have this same discussion ten years ago: when would we have one pill, once a day? Now it’s here and working for the majority of people.

**Huff:** We need to get to the next generation of HIV drugs that are more tolerable, less susceptible to resistance, more forgiving of dosing lapses, and that have well-understood long-term safety data. Unfortunately, many clinicians are content with the current drugs and complacent about the need for developing a next generation of therapy. So the pharmaceutical industry, attracted by more alluring opportunities in hepatitis, does not see a compelling market demand to invest in new HIV drugs.

**Phair:** You want meds that have minimal metabolic effects, in terms of fat distribution, lipids, glucose, and blood pressure – all of which are seen with the current drugs. In the MACS, we’ve seen a rise in blood pressure in people who have been on HIV meds for more than two years. And some problems of aging are worsened by these meds. For example, Viread does not seem to cause kidney problems in younger people, but when you give it to an older person you’ve got a potential problem, because renal function is already diminished.

I’d agree if the meds were as benign as Tic Tacs, but until then it’s a complex risk/benefit decision. I’m a little surprised when I hear someone suggest we have good long-term data that the newer agents are less toxic. We only have short-term data.
**Bookhardt-Murray:** Absolutely. A better side effect profile, and number of pills, number of times a day. Even one pill once a day is a barrier for some people. In fact, some people can’t get that pill down – it’s too big. That’s a barrier. If there were injections, implants, sublingual meds, a liquid that doesn’t taste so bad – all that would help with adherence.

**Do you think our view of HIV as a disease only of immune suppression is changing?**

**Phair:** I think that immune activation and inflammation are going to be as important as immune suppression, but we don’t have the data to tell us which inflammatory markers to watch. I do think we need to understand the inflammatory state of a person on therapy, even if they’re virally suppressed. But I’m loathe to put someone who is controlling their viral load without drugs on HIV meds – so you’re asking the right question, I just don’t have the answer.

**Huff:** HIV does a lot more than kill T cells. It causes irreparable damage to the immune balance within days of infection by wiping out a key population of T cells in the gut and elsewhere. Viral replication causes ongoing damage, probably due to chronic immune activation and inflammation. And there is low-level toxicity from HIV proteins that are released even in people with undetectable viral loads – if these proteins send signals to the immune system, improper immune responses may continue.

**Vail:** That’s why I think some people are saying to treat everybody. It’s about treating an infection that’s causing inflammation and organ damage. The guidelines do say that it doesn’t matter what your CD4 count is if you have kidney disease, you should treat. If you have cardiovascular disease, treat. If you have HBV, don’t treat that without treating HIV.

**Brown:** Yes. We know that HIV depletes the gut immune system very early and that there are more subtle effects of nutrient absorption – but at what stage is that having important effects? Does it reverse with improved CD4 counts? There are things that are continuing to happen even in people on treatment with a well-controlled infection. People who smoke have double the risk of lung cancer if they also have HIV – what causes that? Would earlier treatment help with that? We don’t know.

**Jefferys:** It’s complicated because the risk of illness from inflammatory diseases is far lower than the risk from immune deficiency. The SMART data are an example: over 95% of the people who interrupted treatment did fine; it’s just that there was a higher risk of illness compared with those who didn’t interrupt. My guess is that START is going to end up with the same sort of finding – starting earlier will be associated with a 50% reduction in the risk of illness, but in absolute terms that means 2% of people in the deferred treatment group will get sick versus 1% of people in the immediate group.

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One encouraging development — it’s deja vu all over again — is that studies are starting to revisit antiinflammatories like aspirin, from the perspective of their impact on things like arteriosclerosis instead of their effect on CD4 counts or other markers that may not fully capture their benefit.

Where do you see HIV treatment being 10 years from now?

**Phair:** I would bet we’ll be treating earlier — we may be starting at diagnosis — with drugs that are less toxic. But unless something dramatic happens that I don’t know anything about, I don’t think we’re going to have a treatment that can eradicate HIV. Eradication of this virus is a very difficult task. I’m skeptical that we will achieve it in the next ten years, but hopefully in 20 or 25.

**Jefferys:** I wish I could predict an immune-based therapy or some treatment that would allow people to dispense with regular meds, but there isn’t really anything I could imagine being available in ten years. People build up more dysfunctional HIV-specific T cells over time and if there were a way of switching them back on, the effects could be quite dramatic — an immunological blitzkrieg on HIV. Researchers are also looking at whether it’s be possible to make people more like mangabeys — in that monkey species, HIV replication doesn’t cause immune activation, so there’s no progression to immune deficiency.

**Gulick:** I would guess we’ll be offering treatment to everyone with HIV. If you could treat everybody with HIV, we could perhaps wipe out the epidemic. The reason is that if someone reduces their viral load to very low levels, it’s much less likely they’ll pass the virus onto someone else. So if you model that on a worldwide basis, eventually the number of HIV cases declines until it goes away. The Swiss cohort idea that you don’t have to use protection if your viral load is undetectable has been debunked, so people still need to take precautions even if their viral load is undetectable. But we do know that the biggest group of people that spread HIV is those who don’t know they’re infected.

**Huff:** Once-a-month dosing could help people with adherence problems or be a good strategy for treating people at high risk of infecting others. And even though the current drugs are effective and tolerable, the long-term effects are not known. For example, almost everyone takes Epivir, but there’s almost no comparative safety data that might reveal subtle toxicity, because everyone takes it. Nuke-sparing studies now under way might tell us if this class of drugs is linked to the signs of premature aging seen in people with HIV.

**Vail:** I think we’ll absolutely be treating earlier, unless we get some nasty surprises. But barring some new information that our newer drugs have some long term toxicities, I think we’ll be treating earlier. We’re smarter than we were ten years ago, but we’re not as smart as we think we are, which is why I think we’re just not ready to treat everyone yet. As a provider, I have to be driven by the person in front of me — but there is a greater issue. If we lower community viral load, there will be fewer new infections, and that should be part of the discussion.

**Bookhardt-Murray:** Ten years from now, we are going to have a cure. Whether it’s an intensive cocktail, or new meds, or an injection, I am convinced we’re going to have a cure. I’m still seeing one or two deaths a month — usually in people who were diagnosed late. They have an undetectable viral load, their CD4 count is up, they look pretty on paper — but they started out with a very low CD4 count and now they’re dying from things like cancer and heart disease. It’s too much — we’ve got to pick up the pace.

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Hepatitis C: The Changing Picture

As if having HIV weren’t already enough of a challenge, about 25% of people with this virus also have the hepatitis C virus. Over time, this can lead to serious liver disease, and some studies show that this happens faster in people who also have HIV.
In addition, people with both HIV and hepatitis C virus (HCV) may not respond to HCV treatment as well as people who have HCV only. But many coinfected people have good treatment outcomes, and effective HIV treatment may slow liver disease progression. Promising new HCV treatments are now in the final stages of development, but these drugs also need to be tested in people with HIV.

Transmission

Like HIV, HCV can be transmitted through direct blood-to-blood contact – sharing needles, for example. Many people were infected through blood transfusions before screening of the blood supply began in 1992. Often, however, the transmission route is unknown.

The CDC estimates that about 3 million people in the U.S. have HCV. Fortunately, the rate of transmission has fallen dramatically since its peak, with new infections declining steadily after 1992 and leveling off in 2003. A CDC study of 5,000 injection drug users in four cities found that the number with HCV fell from 65% in 1994 to 35% ten years later. But many people who were infected decades ago are just now starting to reach the advanced stages of liver disease. And, because hepatitis C usually has no symptoms in its early stages, people often don’t know they carry the virus.

Their risk of dying from liver disease are both now starting to fall, thanks to fewer new infections and better HCV treatment. Spanish researchers, for example, recently reported that while 71% of people with HIV entering their study in 1997 had HCV, only 16% did in 2006, largely due to fewer injection drug users becoming infected.

It used to be thought that HCV was rarely transmitted through sex, based on studies of long-term, monogamous heterosexual couples. Since the early 2000s, however, doctors in Europe have reported outbreaks of HCV that appear to be sexually transmitted. These mostly involve HIV-positive gay and bisexual men, though there have been a small number of cases in HIV-positive women and HIV-negative men. Similar outbreaks have been reported in Australia and the U.S.

A study done at a British sexual health clinic found that men with HIV were 13 times more likely than HIV-negative men to have HCV. A similar study at a clinic in Amsterdam found that 18% of gay men with HIV also had HCV, compared with less than 1% of HIV-negative gay men. While the risk factors vary from study to study, these outbreaks have been linked to unprotected anal sex, fisting, sex toys, multiple sexual partners, sex in group settings like bathhouses, using recreational drugs during sex, and having other STDs. While some HCV may be present in semen, experts suspect most transmission during sex is probably the result of contact with small amounts of blood.

A recent analysis of more than 200 men in the U.K., Netherlands, Germany, France, and Australia who were diagnosed with acute hepatitis C between 2000 and 2006 found evidence of HCV transmission within sexual networks. Genetic analysis showed that most of the men had closely continued on next page
related virus, and about a quarter of them had HCV genotype 4, which is uncommon in Europe – further evidence of a sexual network of transmission.

**Disease Progression**

Over years or decades, HCV can lead to advanced liver disease, including cirrhosis and liver cancer. Many studies have found that people with HIV tend to experience faster disease progression than their negative counterparts. Coinfected people are more likely to have liver fibrosis (scarring) than people with HCV alone, and the degree of damage can be worse. But recent reports suggest that people whose HIV is well controlled by meds and who have higher CD4 counts may not have worse liver disease outcomes than people who do not have HIV.

Some of the most worrisome findings come from Daniel Fierer, MD, at Mt. Sinai in New York City. He first reported at the 2007 Retrovirus conference that a small group of HIV-positive gay men recently infected with HCV seemed to be experiencing unusually rapid liver disease progression. As reported in the Journal of Infectious Diseases, liver biopsies of 24 men found that one had serious stage 3 fibrosis (on a scale of 0 to 4), 18 had moderate stage 2 fibrosis, three had mild stage 1 liver damage, and two showed no evidence of fibrosis (stage 0). A related analysis found that even the few men who were able to clear HCV without treatment still had moderate fibrosis.

These results were quite surprising, since the men had shown signs of HCV infection for only about four months. Dr. Fierer’s work suggests that having HIV at the time of HCV infection may promote rapid liver damage. This was the case even though his patients had well-preserved immune function, with a median CD4 cell count of 535, and more than 90% had an undetectable HIV viral load. Researchers studying the acute HCV outbreaks in Europe have not reported similar findings, but they mostly use the less accurate FibroScan method instead of liver biopsies to estimate fibrosis.

**HIV Treatment**

The reasons for faster fibrosis progression in people with HIV are not well understood. Once recent laboratory study showed that HIV can enter specialized cells in the liver and trigger them to produce scar tissue. In addition, the risk of liver toxicity from HIV drugs can be higher in people who also have HCV. On the other hand, two of the drugs most commonly associated with liver damage – Videx and Zerit - are no longer widely used.

Other research suggests that the immune system activation and inflammation caused by ongoing HIV replication contributes to liver disease progression. In the SMART study, people who stopped HIV meds when their CD4 count fell below 350 were more likely to develop serious liver disease than those who stayed on continuous therapy. Furthermore, recent research shows that HIV treatment slows fibrosis progression and may even help reverse liver damage. Jose Pascual-Pareja from Spain reported in AIDS that in coinfected people with CD4 counts above 350, HIV treatment was associated with reduced liver inflammation and cell death, which in turn was strongly associated with less fibrosis.

Other evidence indicates that HIV treatment may not completely reverse the effects of HCV. A University of Toronto analysis of 17 studies (3,567 people) found that coinfected people not taking HIV meds were about 2.5 times more likely to develop cirrhosis than people with HCV alone. But the risk remained 1.7 times higher even for those taking HIV meds. Similarly, a recent French study showed that advanced liver fibrosis or cirrhosis was twice as common in coinfected people, compared with people with HCV only (39% vs. 18%), even though most of the former were taking HIV meds and their average CD4 count was nearly 500.

Finally, an analysis of repeated liver biopsies from 47 coinfected people in Virginia (mostly on HIV meds with an average CD4 count of about 600) found...
that 33% saw their fibrosis worsen, 44% saw no change, and 21% saw their fibrosis improve. There was no link between progression and baseline liver damage, CD4 count, use of HIV meds, or response to HCV treatment. Because no obvious factors predicted worsening fibrosis, the researchers recommended that all coinfected people should be offered HCV treatment since it is not possible to tell who will progress.

**HCV Treatment**

Current treatment for HCV is pegylated alpha interferon injections (Pegasys or PegIntron) once a week plus twice-daily ribavirin pills. Most people in the U.S. have HCV genotype 1, which is harder to treat than genotypes 2 or 3. African-Americans do not respond as well as whites, but we don’t know why. Latinos may respond slightly less well than non-Hispanic whites, while Asians seem to do better.

Interferon can cause difficult side effects, including depression, fatigue, and low white blood cell count, and ribavirin can cause anemia. Many people are reluctant to start treatment for this reason, but not everyone has these side effects and they can often be managed. Recent studies, for example, have demonstrated the benefits of drugs that stimulate blood cell production and of starting antidepressants before the interferon.

About 20% of people with HCV will clear the virus without treatment, though this occurs less often in people with HIV. If treated soon after infection, cure rates are very high for both coinfected people and those with HCV alone. Among the men with new HCV infections in the Mt. Sinai study, for example, 80% who were treated for six months had a sustained virological response (SVR — an undetectable HCV viral load six months after finishing treatment), which most likely means they were cured.

The standard length of treatment is 48 weeks for genotypes 1 or 4 and 24 weeks for genotypes 2 or 3. Current guidelines recommend that coinfected people be treated for 48 weeks regardless of genotype, but recent research shows that 24 weeks appears adequate for those with 2 or 3.

As a group, coinfected people do not respond as well to treatment as those with HCV alone. This may be because interferon works by stimulating the immune system, which is weaker in people with HIV. On the other hand, some recent studies show that coinfected people with well-controlled HIV and high CD4 cell counts can achieve results almost as good as those for HIV-negative people.

In the APRICOT trial, about 40% of coinfected people with HCV genotype 1 and about 60% of those with genotypes 2 or 3 achieved an SVR using peg-interferon plus ribavirin. This compares with about 50% and 75% in studies of HIV-negative people. Similarly, in the Spanish PRESCO trial, 36% of coinfected patients with genotype 1 and 70% with genotypes 2 or 3 achieved sustained response.

The impact of coinfection on treatment response seems to vary based on HCV genotype. In a recent Swiss study, coinfected people and those with HCV alone had similar SVR rates if they had genotype 2 or 3. But among people with genotypes 1, 4, or 5, many more people with only HCV achieved an SVR (58%) compared to coinfected people (13%).

In an effort to improve response rates and reduce side effects, researchers have studied different doses and durations of treatment. It is difficult to summarize this research, since the data are mixed and sometimes contradictory. While higher doses generally offer little extra benefit, extending treatment to 72 weeks may improve response in some coinfected people. People who do not have a substantial drop in HCV viral load within 4 to 12 weeks are unlikely to achieve an SVR and are usually advised to stop treatment.

While it is clear that people who achieve an SVR lower their risk for cirrhosis and liver cancer, the best course for nonresponders is less clear. The HALT-C trial of people with HCV alone showed that long-
Life and Death and HIV on Long Island

by Lycia Davis

I grew up on Long Island and I spent most of my life there. When I was diagnosed with HIV in 1992 I didn’t feel sick, but I was prescribed AZT. I was extremely nervous about taking it because there was such a negative stigma associated with HIV on Long Island. The information from AIDS organizations in New York City had not made its way out there. Many people still believed that HIV was a punishment for specific groups of people, like drug users and prostitutes. I had always heard horror stories about people dying from AIDS, and I personally knew at least 30 people who had passed away.

My husband kept trying to convince me that I wasn’t positive, and that AZT was killing people faster than HIV, so I might as well stop taking it.

To my knowledge there are very few organizations or medical programs that provide services to people with HIV on Long Island. For example, one of the HIV programs that I attended was on the “infectious diseases” floor of a hospital. It was inevitable that when you stepped into the elevator in that hospital and pressed the button for the “infectious diseases” floor that someone would assume that you are going to that floor to receive HIV treatment. Not everyone in that elevator would know that the HIV programs were housed on that floor, but it was something I worried about. I also remember seeing people from my neighborhood in the waiting room at the hospital which caused me to worry if they would disclose my status without my consent.

Many of the organizations that served people with HIV did not offer much privacy, or the name of the agency made it clear what type of services they provided. Because it was not as easy for me to feel safe and somewhat anonymous at these organizations, I stopped going.

It was extremely difficult for me to feel stable while trying to keep a strict medication regimen, working full time, taking care of my son and a mentally ill father, and avoiding my abusive husband.

My husband kept trying to convince me that I wasn’t positive, and that AZT was killing people faster than HIV, so I might as well stop taking it. I couldn’t help believing what he said — I was in a state of denial myself and I was using drugs. I stopped taking the AZT. At that time because I was healthy I thought I could just take my chances without meds instead of enduring the side effects of AZT. I also thought, in a twisted way, that if I didn’t take my meds then I wouldn’t have to admit that I was positive.

Even though my husband had convinced me that I wasn’t positive, deep in my heart I knew that I was. I was just so scared of what that would mean for me. I remember sitting in the waiting room at the hospital waiting to see my doctor and noticing how so many of the other people in the waiting room had discolored skin. I couldn’t help but think that I would begin to look like that after taking AZT.

In 1996, after a number of years without taking AZT, I developed a severe case of pneumonia. I needed thoracic surgery to repair my collapsed lung. I was in a great amount of pain and at death’s door. After I made it out of surgery my doctor suggested that I have an HIV test. In the back of my head I already knew that I was positive, but I hoped that maybe my first diagnosis was a mistake.
So I traveled to Hempstead to get an HIV test for the second time, and I tested positive. At this point I finally admitted to myself that I had HIV. Soon after that – after I found out that my CD4 count was 77 and my viral load was 55,000 – my doctor prescribed Combivir. My CD4 count began to go up, even though one of my meds, Norvir, was horrific. It was only available in a liquid form in 1997, and the only way I could stomach the awful taste was for my son to force-feed it to me with a spoonful of chocolate Nutella.

At the time I was working in the health care field, but I continued to use drugs to get high. Then my husband became violent toward me. It was extremely difficult for me to feel stable while trying to keep a strict medication regimen, working full time, taking care of my son and a mentally ill father, and avoiding my abusive husband.

In 2000 my doctor put me on Sustiva and Truvada. This regimen was much easier for me, as it cut me down to one dose a day, which was a welcome relief. I also stopped using drugs in 2000 and have been clean ever since. Then in 2005 I began taking Atripla, and I haven’t had any severe side effects with Atripla. Later that year, I came across a flyer for a positive relationships support group and started attending. I met so many people who were living long, fulfilling lives even though they were positive. I didn’t experience anything like this before and it gave me hope that there was life after HIV. I had finally come to terms with my status through the guidance I received from other HIV+ people that participated in these programs. The friends that I made gave me the extra support I needed to leave my abusive husband.

After I left him in 2006 and moved to Brooklyn I became a client at several agencies in the city and continued attending support groups for people living with HIV. While I was living on Long Island I only heard about people dying from HIV. Once I moved into New York City, I met so many people who were living long, fulfilling lives even though they were positive. The agencies that I began receiving services from provided me with endless support, along with new friends and peers to help guide me through life with the virus.

My son has been a guardian angel throughout my struggle in coming to terms with being positive. He found out that I had the virus when he came across some medical papers of mine, and has been at my side ever since. When I was in the hospital with pneumonia he took it upon himself to research what types of treatments were available for me, and he was only 17 at the time. He has been such a strong advocate for me over the years, and continues to support me on my journey to wellness.

Not only have I been able to take advantage of services by several organizations in the city, but I was given the opportunity to represent GMHC at the annual National Conference on African-Americans and AIDS. I attended several workshops and collected materials to bring back to the groups that I attend. I am thankful to be on my way out of a place of denial and on my way to a bright future that provides me with opportunities to empower myself while living with HIV.
The Skinny on Body Fat and HIV

by Nelson Vergel

Some people with HIV complain of weight and belly fat gain after they start HIV treatment. But researchers have not been able to determine what causes the problem. Some studies actually dispute that there is a problem, and say that people with HIV do not have more visceral fat than HIV-negative people. But the HIV community as a whole has come to accept the fact that body changes happen to some people living with this virus. The problems associated with increased visceral fat include poor body image, depression, bloating, fatigue, sleep apnea (breathing problems), and possible heart problems. It not only affects the way people look – it could lower their chances of long-term survival.

Fortunately, the HIV meds most often linked to these problems are no longer commonly used, and newer meds are less likely to lead to changes in body shape and fat metabolism. Data from several studies, including the Swiss HIV Cohort Study, showed that the use of drugs like Zerit and Retrovir (AZT) declined sharply from 2000 to 2006, along with the number of people who experience body changes.

Lipodystrophy (abnormal fat distribution) has been reported in many HIV studies. It includes one or more of the following: lipoatrophy – a decrease in the subcutaneous fat directly under the skin (associated mostly with the use of Zerit or AZT); lipohypertrophy – an increase in the visceral fat deep in the belly; increases in bad (LDL) cholesterol and triglycerides; and decreases in good (HDL) cholesterol, sometimes with an increase in blood sugar. The majority of people taking HIV meds do not experience any body shape changes, but some experience one or more of these metabolic complications. A 2007 meta-analysis of several studies estimated that between 14% and 40% of people taking HIV meds have some form of lipodystrophy.

The Multicenter AIDS Cohort Study (MACS) recently reported that men with HIV in general weigh less than HIV-negative men, but their visceral fat is about the same. Most men with HIV were thinner due to subcutaneous fat loss in the arms, legs, and buttocks, but had as much internal belly fat as the heavier HIV-negative men.

Fortunately, there have been advances in our understanding of lipoatrophy. We now know that it is often linked to the use of Zerit or AZT, and there are two FDA-approved treatments for facial lipoatrophy: Sculptra and Radiesse. However, the same cannot be said about lipohypertrophy, which seems to be caused by many factors. Researchers have not been able to blame any specific drugs. Several studies report that people starting standard HIV combinations have an average increase in visceral fat of 15% after 96 weeks.

It was first thought that protease inhibitors were the main culprits of belly fat gain, but several studies that did not include protease inhibitors also showed increases in visceral fat. An analysis of people in the French APROCO study found that those who started HIV meds with lower CD4 counts gained more visceral fat, possibly due to the large change in their CD4 counts. An analysis of a study comparing Aptivus to Kaletra showed that when taken with Viread and Epivir, the drugs did not increase visceral fat in those who start them with a CD4 count above 250. Some other studies have shown that people who start a protease inhibitor or non-nucleoside along with Zerit, AZT, or Videx seem to have more visceral fat gain than those who start them with other nucleosides. So, the bad guys linked to lipoatrophy may also worsen belly fat.

Switching from a protease inhibitor to Sustiva or Viramune while taking Zerit or AZT has not helped in lowering visceral fat. But a recent small study showed that people who switched from Kaletra to Reyataz while taking Truvada had a decrease of 15% in visceral fat after 6 months. So, we may start to see differences in how HIV meds affect the body when taken with newer nucleoside analogs like Truvada.

An analysis of people in the French APROCO study found that those who started HIV meds with lower CD4 counts gained more visceral fat, possibly due to the large change in their CD4 counts.

14 SUMMER 2009 achieve
Insulin resistance is linked to fat gain, regardless of HIV status. Insulin is a hormone produced by the pancreas, and controls blood glucose (sugar). It captures glucose and pushes it into muscle tissue where it is stored as glycogen for later use as energy. Protease inhibitors may interfere with that process. Also, some people may have a genetic predisposition to insulin resistance. Zerit, AZT, Crixivan, higher doses of Norvir, and most protease inhibitors have been shown in lab studies to impair the action of insulin. This may be a part of the puzzle, but not the entire explanation for visceral fat gain. Aging, poor diet and a lack of exercise may make someone more prone to lipohypertrophy, but people who follow a healthy diet and an exercise program may still suffer from this problem.

What To Do?
Several treatments and approaches have been and are being studied:

**Human growth hormone** can lower belly fat, but not without side effects. Serostim (a brand of HGH) is approved to treat HIV wasting, but its side effects led the FDA to deny its approval for lipodystrophy. These included joint pain, edema (water retention), increased lipoatrophy and blood sugar increases. Its high cost and lack of insurance reimbursement (due to its lack of FDA approval) are also barriers to use. It requires daily or every other day injections under the skin. But it has been shown to decrease visceral fat by 30% in 6 months.

**Tesamorelin** is a copy of a hormone that causes the pituitary gland to produce growth hormone. It will soon be up for FDA approval, but, as with Serostim, the FDA may deny approval if no health benefits are seen. Like Serostim, it requires daily injections under the skin but it seems to have milder side effects: mild edema, some joint pain, and a hypersensitivity reaction in 10% of people (sweating and rash). But it does not increase blood sugar or cause lipoatrophy, and it may lower triglycerides, a problem caused by some HIV meds. It has been shown to decrease visceral fat by 15% in 6 months.

Activists are concerned that its price will be high. This could cause insurance companies and Medicare to deny payment since it may be perceived as a cosmetic product. Also, it will be sold in the U.S. by Serono, the same company that sells Serostim. Serono has had poor relations with activists in the past, and was also fined over $700 million by Medicare for using fraudulent practices to induce some physicians to prescribe Serostim.

**Leptin** is another new contender in the search to decrease visceral fat. This hormone, discovered in 1994, is produced by fat cells. Leptin levels in the blood are generally proportional to the level of body fat. In the hypothalamus (the part of the brain that controls appetite), high levels of leptin suppress the appetite and stimulate fat-burning. Like Serostim, it is taken as an injection under the skin, but it requires two injections a day, though other doses may be studied in the future. In a study of eight men with HIV and lipodystrophy, visceral fat decreased by 32% after 6 months, with no change in subcutaneous fat. Bad (LDL) cholesterol decreased by 16% and good (HDL) cholesterol increased by 19%, with a significant decrease of triglycerides. Leptin was well tolerated but it decreased lean mass. Early, small studies have not shown leptin to have negative effects on blood sugar, as Serostim can. But activists are asking its manufacturer to do larger studies in people with HIV to determine if leptin is useful and if it will be cost-effective.

**Metformin** is a diabetes drug that at first showed promise in reducing abdominal fat. But later studies have not confirmed this, and have in fact shown that it may
worsen lipoatrophy. However, in people without lipoatrophy who have glucose intolerance, metformin may reduce the risk of diabetes and therefore, abdominal fat. Its effects may be enhanced by exercise. Metformin improves insulin sensitivity, triglycerides, and fatty liver, but can cause diarrhea and weight loss (which may itself lead to a decrease in visceral fat). Some people have reported low blood sugar and dizzy spells, so users of this drug should have snacks at hand to increase blood sugar if needed.

**Testosterone gels** (Androgel, Testim) can reduce waist size in men, but only by lowering subcutaneous fat. In studies, no visceral fat decreases were seen. Testosterone is usually prescribed for people with HIV who have low blood levels of natural testosterone. Data in women are lacking, but one study of 23 women found that those with HIV-related lipodystrophy had higher testosterone levels than HIV-positive women without lipodystrophy. Gels, injections, and a new subcutaneous pellet delivery system are becoming more commonly accepted by physicians.

**Oxandrin**, an oral anabolic steroid, showed encouraging results for decreasing visceral fat in a small pilot study. But LDL cholesterol increased and HDL cholesterol decreased, along with a small decrease in subcutaneous fat. No body fat studies have been done with the other commonly used anabolic steroid, nandrolone decanoate.

**Nutrition** studies are lacking. A study at Tufts showed a trend toward less lipodystrophy in those who exercised and increased their soluble fiber (fruits and vegetables). More research is needed on low-carbohydrate diets, which have been shown to improve insulin resistance and visceral fat in HIV-negative people. One observational cohort found that people with HIV eat more saturated fats, which could lead to fat problems. A study of nutrition and lifestyle modifications resulted in decreased belly fat in people with HIV, so there is a clear need for more care providers and organizations to include nutrition and exercise information in their educational efforts.

**Aerobic exercise** and **weight training** decreased triglycerides and visceral fat in a small pilot study. Another study showed that strength training increased lean body mass and decreased fat mass more than aerobic exercise, while improving cholesterol and triglycerides. A regimen of an hour of strength training combined with 20 minutes of aerobic exercise three to four times a week has been shown to work for most people (results take at least eight weeks to be noticeable). But exercise research in HIV remains in its infancy. Sticking to an exercise program can be a challenge for many people who lead busy lives or can’t afford to join a gym. But effective home exercise programs are available and could be part of the health counseling given by health care providers and organizations.

**Liposuction**, assisted by ultrasound, seems to be effective at removing fat from the hump that can occur at the back of the neck. Breaking the fat fibers with ultrasound can loosen them up for easier removal. But this can not be used for removing the visceral fat that surrounds organs in the belly, since removing that is too risky. Some insurance plans and Medicare pay for liposuction when the fat gain is associated with pain or sleep disorders.

Fat gain can also occur in the upper part of the body, especially in the breasts. Some studies show increases in estradiol, a female hormone, in men taking Sustiva.
This may cause gynecomastia (increased breast size) in a few people. Drugs like Arimidex, an estrogen blocker, or switching from Sustiva can help those who are in early stages of this problem.

**Fat burners** are being promoted by some TV commercials. But they have not been shown to work and can increase blood pressure and anxiety. Also, beware of nutritional growth hormone supplements—there are no data indicating that they work.

**Measuring Progress**

We know when our bodies are changing by the way our clothes fit. Some people go one step further and measure their body dimensions before starting any new program or treatment.

The full-body DEXA scan is the gold standard test in lipodystrophy research, but is hardly used in clinical practice and cannot differentiate between visceral and subcutaneous fat. It’s very useful since it gives information about fat, muscle mass, and bone density in every part of the body. It’s not expensive (around $130) and is usually covered by Medicare and insurance. It should measure the full body and not just the hip area. Low bone density has also been linked to HIV, so this scan can be useful in detecting early bone changes before fractures happen, but this may not be covered by some insurance plans. A DEXA scan could be considered when someone first tests HIV-positive and then every few years to assess body changes and justify reimbursement for needed treatments. However, there are currently no guidelines for its use in the care of people with HIV.

The best way to assess visceral fat loss is the use of CT scans of the area around the belly button (at the level of vertebrae L4-L5). However, this method is used mostly in research since most insurance companies will not pay for it.

Between 30% and 50% of people with visceral fat may have impaired glucose tolerance (their bodies do not use sugars for energy very well) and may be prediabetic. A glucose tolerance test can reveal that problem. Glucose intolerance has been linked to fat gain, increased triglycerides, and development of diabetes. An improvement in glucose tolerance usually leads to fat loss and better lipids.

**Current Trials**

A few studies are currently enrolling in the U.S. to find the best ways to improve cholesterol, triglycerides, and body composition in people with HIV. More info on these studies can be found online by looking for the words in bold under “Choose a treatment” at trialssearch.org.

- A trial in Houston combines exercise with **Niacin** (a vitamin that may raise good cholesterol), **Tricor** (used to lower triglycerides), and prepared meals to look for improvements in lipids and visceral fat.
- A Boston trial is studying **Avandia** plus **leptin**.
- Another in St. Louis will look at **Actos** with exercise for improving insulin resistance, heart metabolism, and heart function.
- One in Dallas will compare four approaches:
  1. a high carbohydrate vs. a high cis-monounsaturated fatty acid diet
  2. aerobic exercise with dietary advice
  3. omega-3 fish oil capsules
  4. **leptin**

The interventions are aimed at improving elevated lipids, insulin resistance, and diabetes.

- A Los Angeles trial is studying whether switching women from a protease inhibitor or a non-nucleoside like Sustiva to **Isentress** will reduce body fat in six months.
- Another at ACRIA and other sites in New York City is looking at **Serostim** (human growth hormone) with or without **Avandia** to study the effects on visceral fat.
- Finally, a study in Los Angeles is combining **L-carnitine**, a nutritional supplement, with exercise to see if it improves muscle function.

**Conclusion**

There is still much to be learned about visceral fat gains and HIV. The first FDA-approved treatment may be available soon, but may come with the barriers of high cost and limited access. There remains a great need for more nutrition and exercise counseling, building on studies of non-pharmaceutical options that cost little to nothing. As people with HIV grow older, advocacy is needed to push for studies of the effect of HIV and its treatment on the body, and to urge insurance companies to reimburse all treatment approaches. Lipodystrophy is a clinical problem that affects quality of life and possibly long-term survival, and it should not be regarded as purely a cosmetic concern.

Nelson Vergel is a treatment activist and the Director of Program For Wellness Restoration: powerusa.org
The Meds and Me

I have lived in Manhattan for 25 years. I was diagnosed with HIV in 1988, but I’m sure I was positive before then. During the first ten years after my diagnosis I spent very little time thinking about HIV. I was healthy and had a good job and a fulfilling social life to keep me busy. I was doing administrative work at a major investment bank in the city and spent the majority of my time working or having fun.

In 1998 my doctor suggested that I start Epivir, Zerit, and Ziagen. Although I was not sick, my CD4 count was lower than the doctors liked to see, so they put me on meds. I had never been sick until I began taking HIV medications. I was doing fine for a while, but then I started having side effects, like elevated liver function tests and feeling weak. So in 2000 my doctor had me switch to Kaletra, Videx, and Zerit, which I stayed on for about eight years.

I was now working at a law firm and began to experience the side effects of these new drugs. I was plagued with lipodystrophy and gastrointestinal problems. This made it hard for me to do my job, but I felt uncomfortable informing my supervisors about my HIV status. I didn’t want to tell them I was positive for fear I would have problems on the job or be fired. I had no other choice but to power through the side effects and try my best to complete my work.

These medicines gave me stomach pain and other gastrointestinal problems that were almost crippling. As corporate Manhattan was not known for its compassion, I continued to keep my HIV status a secret from my coworkers. The pain got so bad that my doctor even tested me for Crohn’s Disease, and I consulted with a nutritionist to see if there were any foods that I could avoid to stop the pain. I lost 15 or 20 pounds and it began showing in my face. Coworkers began to comment on my appearance.

I had a long conversation with my doctor, and he changed my dosing schedule to one that was much more complicated. I was on the same meds, but now had to take them at three different times each day and keep a very strict eating schedule because the Videx had to be taken on an empty stomach. This complicated drug and meal schedule made it tough to take part in social events unless I had full control of the situation. There was always a risk that my stomach would act up or a mealtime would be rearranged. Someone would offer me a snack and I had to think, “When did I eat last? When is my next dose?” It became so difficult to spend time with friends that I ended up cutting myself off for the most part. I lived the quiet life of a church mouse for quite some time.

I didn’t want to tell my supervisor I was positive for fear I would have problems on the job or be fired. I had no other choice but to power through the side effects and try my best to complete my work.

By early 2008 I was fed up with the side effects. I had lost weight, my body shape had changed, and I had high cholesterol from the medicines and all the food I was eating to gain weight. My quality of life at this point was very low due to all the restrictions the medications put on me. I was tired of enduring years of side effects. I discussed going off the meds with my doctor. He explained that HIV medications had changed a lot since I started, and that maybe it would be a good idea to change some things around. I was thrilled when he agreed it was time for a change, and stopped the HIV meds until we could find a regimen I could live with.

I was intent on researching what worked for my peers so that I could find out which meds were right for me. The research took longer than expected,
and my viral load was climbing and my CD4 count had dropped to 150. I went to GMHC to ask for a case manager, but they wouldn’t give me one because my income was too high. Fortunately, I spoke with some of the treatment adherence staff, and they connected me with other services that I could benefit from.

In early 2009 my doctor suggested that I start taking Bactrim because I was no longer taking any HIV meds and my CD4 count was below 200, putting me at risk of PCP pneumonia and other infections. I started that medicine but had an allergic reaction and was bedridden for several days.

But last March I finally began a new HIV drug regimen. I am now taking Truvada and Reyataz with Norvir. This regimen has given me few side effects, and I am slowly putting weight back on. That’s a pleasant side effect, since I had lost a lot of weight in my arms, legs, and face as a result of my previous regimen. My face has begun to fill in, and I haven’t felt the need for facial fillers. When I first met my doctor, I was going to ask about them but I saw that he had a large birthmark covering half of his face! I felt that if he could live with that, I could handle some sunken cheeks. My non-gay friends don’t seem to be concerned about how I look – it’s only in the gay community that I feel pressure to do something about the way I look.

My relationship with HIV meds has been a tumultuous one, but I think I finally have a good regimen that can keep me healthy.

I still live in my New York City apartment but currently spend several days a week working on Long Island. This gives me the opportunity to spend time with my family and be surrounded by the beautiful scenery on Long Island. For now I am happy with my current regimen. So far, the side effects are minor compared to the benefits. I hope I continue without major side effects so that I can take advantage of the social opportunities that I missed out on in the past ten years. My relationship with HIV medications has been a tumultuous one, but I think I finally have a good regimen that can keep me healthy.

To anyone who is having problems with the older HIV meds, I say switch! The newer ones are less toxic – they still have side effects, but they’re more manageable. And once-a-day dosing is far easier than what I had to go through. I’m getting back into social scene, and particularly want to connect with other people who are living with HIV. I need the kind of support you can get only from people who have been where I’ve been. Stay tuned!
Peering in the Pipeline

More HIV meds could be approved next year – some that come from new classes of drugs and some from already approved classes. Here's a brief look at a few.

by Mark Milano

Blocking the Door
Several drugs are targeting HIV's entry into CD4 cells. The hope is that preventing the virus from even entering the cell will result in less damage to cells and fewer side effects.

Vicriviroc could be the second co-receptor inhibitor to receive FDA approval (the first, Selzentry, was approved in 2007). These drugs interfere with the second step in HIV's entry into a CD4 cell, by blocking the R5 co-receptor.

The VICTOR-E1 study of vicriviroc (in people resistant to other HIV drugs) found that after 48 weeks, 59% of those who added vicriviroc to approved HIV drugs had their viral load drop below 50, compared with 25% of those who took the approved drugs only. Two larger trials in people resistant to other HIV drugs are finishing soon and could report results before the end of the year.

Trials of Selzentry and vicriviroc in people who have not taken HIV meds before have found these drugs to be less effective than Sustiva, but this may have been due to the tropism test used. This test screens out anyone who has HIV that uses the X4 co-receptor, since these drugs will not be effective in those people. But looking back at studies of regimens containing Selzentry using a new, more sensitive tropism test, it was discovered that the drug was as effective as Sustiva in people screened with the more sensitive test.

Both drugs are currently in trials for people who have never taken HIV meds before, using the newer tropism test. Vicriviroc is being studied with Reyataz/ Norvir but no other HIV meds. This is a new approach, since most HIV regimens include nucleosides like Truvada or Combivir. Norvir will not only boost Reyataz levels, but should also increase vicriviroc concentrations 5 to 6 times. Results from this trial could be available in 2010.

Sustiva is currently one of the most effective and commonly prescribed HIV meds, but that could change if newer drugs in its class (non-nucleosides) are approved.

Contenders to the Throne
Sustiva is currently one of the most effective and commonly prescribed HIV meds, but that could change if newer drugs in its class (non-nucleosides) are approved. About half of people who take it develop central nervous system (CNS) side effects like vivid dreams and dizziness in the first two weeks. These usually go away within a few weeks but 4 to 10% of people stop the drug because of them. It may also be linked to fat changes in the body. Intelence, the first new drug in this class in over a decade, was recently approved for people who have become resistant to Sustiva. But three new drugs in this class are worth watching.

Rilpivirine is a once-daily pill that is active against HIV that is resistant to Sustiva. In a two-year study of people who had not taken HIV meds before, it was as effective as Sustiva in lowering viral loads to below 50. But it caused less rash (9% v. 21%) and fewer CNS side effects (31% v. 48%) than Sustiva. Also, triglycerides dropped in people taking rilpivirine but rose in those taking Sustiva. There are

TBR-652 is another R5 co-receptor inhibitor that is just beginning its first study in people with HIV. Early studies have shown that it will likely be taken once a day, will not require Norvir boosting, is well tolerated, and may be more potent than Selzentry.

Ibalizumab (TNX-355) is different from Selzentry and vicriviroc in that it blocks the CD4 receptor on T cells rather than a blocking a co-receptor. This means it could be effective against virus that use either the R5 or X4 co-receptor. It is a genetically engineered monoclonal antibody, made by cloning a single parent cell and producing exact copies that bind to the same CD4 receptor that HIV binds to. It is currently enrolling a Phase II trial that should complete in October 2010.

An earlier study found that people who had taken HIV meds before had greater viral load drops when ibalizumab was added to approved HIV drugs. They also had greater increases in CD4 counts: a rise of 51 vs. 5 for those not taking ibalizumab. The drug is being studied as an infusion given every two weeks, so it's unlikely that a pill form will be possible. If approved, it will probably be used only in people who have become resistant to other HIV meds.
plans to combine rilpivirine with Viread and Emtriva in a single pill, creating a competitor for Atripla (also a three-drug pill). Another study is looking at a form of the drug that is given as an injection once a month.

**IDX899** showed strong antiviral activity in a seven-day study in 32 people with HIV who had not taken HIV meds before. In this short study, side effects were generally mild and were similar to those in people taking a placebo. It may be less prone to resistance than Sustiva (which requires only one mutation for resistance to develop).

**RDEA806** is active against HIV that is resistant to Sustiva, but unlike other non-nucleosides it is not processed by the liver’s P450 system, so it will most likely not interact with other medications that use this system. A small study found significant viral load drops after 8 days in people who had not taken HIV meds before. Another study found that the drug has “a high genetic barrier to resistance,” meaning that HIV must create multiple mutations in order for the drug to stop working.

### Blocking Integration

Researchers began looking for a drug to block HIV’s integrase enzyme in the early ’90s, but several of these drugs failed. Finally, Isentress was approved in 2007 for people who were resistant to other HIV meds, and that approval was expanded in July of 2009 to include those who had never taken HIV meds before. It has been shown to be a powerful drug, lowering viral load faster than other drugs while having few side effects.

Elvitegravir will likely be the second integrase inhibitor to receive FDA approval. Unlike Isentress, it must be boosted with Norvir or a similar drug, and is taken once a day. In a study of people who were resistant to some protease inhibitors, people taking elvitegravir had greater viral load drops than those who took Prezista or Atripla.

The drug is currently being tested as part of a “quad combo” pill that combines it with Viread, Emtriva, and GS 9350 (a new boosting agent that works like Norvir). If approved, it could challenge Atripla in the “one pill, once a day” category. A study comparing the two regimens in people who have never taken HIV meds is underway.

**GSK 1349572** is a new integrase inhibitor whose first results were reported at the IAS conference in July of 2009. It may lower viral loads even more quickly than Isentress or elvitegravir. In a study of people who had not taken an integrase inhibitor before, 7 of 10 people taking the highest dose of the drug (and no other HIV drugs) achieved an undetectable viral load within 10 days. Unlike Isentress, it is taken once a day, and unlike elvitegravir, it does not require a boosting agent.

**Bevirimat** could be the first HIV “maturation inhibitor.” Like protease inhibitors, maturation inhibitors interfere with the final processing of newly made HIV proteins, but these drugs bind to the gag protein rather than to the protease enzyme. The resulting virus particles have defects that make them unable to infect other CD4 cells.

Generally, when a first-in-class drug becomes available, few people have resistance to it. But recent studies have found that bevirimat is not effective in some people whose virus is resistant to protease inhibitors. A study that screens out people who have certain gag mutations is planned to start later this year.

While none of the above drugs appear to be major breakthroughs, they would bring us closer to the goal of effective, easy-to-take regimens that have fewer side effects. While we wait for a cure, these new meds could mean that people with HIV will find it easier to live with and control their virus.

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term maintenance therapy with low-dose peg-interferon reduced HCV viral load and liver enzymes, but that did not translate to lower rates of cirrhosis, liver cancer, or death. At the 2008 Retrovirus conference, the SLAM-C trial likewise reported that maintenance therapy did not prevent fibrosis progression in coinfected people.

The only treatment for end-stage liver disease or advanced liver cancer is a liver transplant. Several studies have shown that HIV-positive liver or kidney transplant recipients with well-controlled HIV and higher CD4 counts do nearly as well as HIV-negative patients. But in coinfected people, HCV almost always reinfecst the new liver, leading to complications and shorter survival.

**New Drugs**

Because of the limited response rates and difficult side effects of interferon, researchers are studying new types of drugs that directly target different stages of the HCV lifecycle. Further along are the HCV protease inhibitors telaprevir and boceprevir. The PROVE 1 and 2 studies included nearly 600 people with HCV only, who had genotype 1 and had not taken treatment before. They took telaprevir and peg-interferon, with or without ribavirin. People who took all three drugs had the best chance of an SVR – around 65%, compared with about 45% for standard treatment. In PROVE 1, the benefit of telaprevir was especially large for African-Americans. A 24-week regimen worked nearly as well as one that lasted 48 weeks, but 12 weeks was too short, and omitting ribavirin increased the relapse rate. People taking telaprevir were more likely to drop out due to side effects, including skin rash and anemia. The PROVE 3 trial enrolled relapers and nonresponders, and about half of those taking the best telaprevir regimens achieved an SVR, compared with just 14% of those taking standard treatment. In this study, the shorter regimens had higher relapse rates, leading the researchers to conclude that treatment-experienced patients might need longer treatment.

In the SPRINT-1 trial, about 600 people with genotype 1 who had not taken treatment before took boceprevir, peg-interferon, and ribavirin. People who took peg-interferon and ribavirin for a 4-week “lead-in” period before adding boceprevir for 44 more weeks had an SVR rate of 75%, compared with 38% for those taking standard treatment. Those who took a lower dose of ribavirin were more likely to relapse.

Several other new drugs are also being studied, including HCV polymerase inhibitors and entry inhibitors. For the near future, treatment with the new drugs will still include peg-interferon and probably ribavirin, although the length of treatment may be shortened. But in the longer term, HCV treatment may start to look more like HIV treatment.

The INFORM-1 study was the first to combine two new HCV drugs without peg-interferon or ribavirin – the protease inhibitors R7227 and the polymerase inhibitor R7128. At the end of this 14-day study, 25% of those taking the highest doses had an undetectable HCV viral load. As with HIV, combination therapy should reduce the risk of drug resistance.

So far, these new drugs have not been studied in people with HIV. This is an important research need, since coinfected people may have faster disease progression and a more urgent need for treatment. It is also important to see if there are any interactions with HIV meds, good or bad. Some early studies suggest there may be drugs that work against both HCV and HIV (for example, the cyclophilin inhibitor Debo 025), so future HIV regimens might include drugs that fight both viruses.

**Conclusion**

While new drugs are eagerly awaited, many people who could benefit from current treatment are not getting it. A recent survey of patients receiving care from the Veterans Administration found that while most needed treatment, only 14% of coinfected people and 22% with HCV alone actually received it.

Many doctors are reluctant to treat HCV in current or former drug users. Several recent studies show that people on methadone maintenance and even active users can achieve good treatment outcomes if they have the support they need to stay adherent. Even as we learn how to improve HCV therapy with better strategies and new drugs, it is crucial to offer the best treatment available now to those who need it.

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The election of Barack Obama inspired a great deal of hope for long-delayed progress on HIV policies and for equality for lesbian, gay, bisexual, and transgender (LGBT) people. His promises included a commitment to ending the ban on federal funding of syringe exchange programs, moving funds from ineffective “abstinence-only” programs to comprehensive sexual health programs, repealing the U.S. entry ban on people with HIV, and developing a first-ever national AIDS strategy.

During the campaign, Obama promised to expand the President’s Emergency Plan For AIDS Relief (PEPFAR) by $1 billion a year for five years. But Obama’s 2010 budget provided only a 2% increase – essentially flat funding the program. He also vowed to make fair-share contributions to the Global Fund to Fight AIDS, TB, and Malaria. Based on the size of the U.S. economy, our fair share is $2.7 billion. But Obama’s plan flattines support at $900 million. Obama’s “Global Health Initiative” reflects bold ideas to expand U.S. support to maternal and child health, sexual and reproductive rights, etc., but the budget largely moves money from one column to another. This would simply change who dies of what cause. We need a true commitment to improving global health through expanded goals and funding.

Activists continue to run up against roadblocks in the fight to lift the 1998 ban on federal funding for syringe exchange. Needle sharing accounts for more than 14% of new HIV infections each year in the U.S., and syringe exchange programs can dramatically reduce that number. In New York City, syringe exchange resulted in a 78% reduction in new HIV infections from 1990 to 2002. But Obama’s 2010 budget retained the ban. The White House website had stated, “The President also supports lifting the federal ban on needle exchange, which could dramatically reduce rates of infection among drug users,” but those words were stripped from the site in May. Fortunately, in July the House Appropriations Subcommittee voted to overturn the ban, but then added an amendment forbidding the operation of exchange programs within 1,000 feet of a school, park, playground, swimming pool, daycare center, video arcade, or youth center. This means it will be virtually impossible for federally funded syringe exchanges to operate in any urban areas. We need the President to keep his promise and remove this program-killing restriction.

Obama’s 2010 budget eliminated several funding streams for abstinence-only sex education programs, and recommended redirecting $115 million into an evidence-based teen pregnancy prevention initiative. While this is a positive move, many worry about its narrowed scope and hope to see funding for comprehensive sex education aimed at all young people, including young gay and bisexual men, who are at an elevated risk for HIV.

Another major development is the proposed removal of the ban on noncitizens with HIV entering the country, which also prevents nonresidents living in the U.S. from achieving most types of legal status. In July 2008, Congress removed it from the Immigration and Nationality Act. In July of this year, the Health and Human Services Department published a proposed rule change to remove HIV from the list of diseases that prevent noncitizens from entering the country. This is the last step needed to end this discriminatory policy. Terminating the ban will also reduce HIV stigma and promote public health by encouraging people to get tested, disclose their HIV status, and bring their HIV meds with them when visiting the U.S.

Nearly 500 organizations and 2,000 individuals around the country have endorsed the call for the government to develop a national AIDS strategy. The U.S. requires countries seeking assistance through PEPFAR to have such a strategy, but the U.S. has never had one itself. The newly appointed Director of the Office of National AIDS Policy, Jeff Crowley, has stated his intention to design a strategy that mirrors the President’s three goals: reducing HIV incidence, increasing access to care, and reducing HIV-related health disparities, especially in communities most vulnerable to infection.

But when it comes to LGBT rights, many are frustrated by Obama’s early record. Promises to repeal both the Defense of Marriage Act (DOMA) and the U.S. military’s “Don’t Ask, Don’t Tell” policy were among the items dropped from the White House website. The Justice Department recently filed a brief defending DOMA which contained legal arguments that – if pursued by the courts – could greatly damage LGBT rights. Obama has also not acted on his expressed opposition to “Don’t Ask, Don’t Tell,” and gay Americans continue to be drummed out of our military.

In sum, in the first six months of the Obama presidency, progress has been made toward better HIV policies. This is less true, however, of policies to advance LGBT equality. While Obama expanded some domestic partner benefits to gay federal workers, many LGBT activists are frustrated at the President’s slow pace toward fulfilling important campaign promises. It is essential that we keep up the pressure on the Administration and the Congress to adopt equitable and effective public policies.
Free HIV Trainings

ACRIA offers free HIV-related trainings in NYC as a NYS DOH AIDS Institute Regional Training Center.

For a list of all the trainings, visit acria.org and click on “Training Calendar.” To download a registration form, click on “Training & Registration.”

You may also contact Gustavo Otto for more information at 212-924-3934, x129.

For listings of all trainings offered by the NYS DOH AIDS Institute, visit:
www.nyhealth.gov/diseases/aids/training

Needle Exchange Now!

A CALL TO ACTION

For the first time in 11 years, the U.S. House of Representatives lifted the ban on federal funding for syringe exchange programs. But this important step forward was tempered by a hostile amendment that restricted such funding: no federally-funded syringe exchange can operate within 1,000 feet of a school, park, playground, swimming pool, daycare center, video arcade, or youth center. This effectively maintains the ban for all urban areas! Congressman Obey called it unworkable. Call your member of Congress and Appropriations Chairs Daniel Inouye and David Obey, and tell them:

“Remove the 1,000-foot restriction on syringe exchange programs so they can operate wherever needed to save lives.”

Senator Daniel Inouye: 202-224-3934
Congressman David Obey: 202-225-3365