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spring
2006

What's New?

25 years after AIDS was first identified, development of new drugs has seen a sudden upsurge. While only one new drug was approved in the last two years, a number of compounds are now moving into advanced trials, offering new hope for people who have become resistant to many of the approved HIV medications

In this issue of *ACRIA Update*, a number of seasoned HIV treatment activists present the “inside story” on the development of HIV drugs, from both activist and personal perspectives. And we’re pleased that former ACRIA staffer Donna Kaminski has weighed in with news from a recent AIDS conference.

Of course, taking any experimental treatment comes with risks, including the risk of adding only one new drug to a failing regimen. ACRIA has always urged anyone who is thinking of joining a clinical trial, either here at ACRIA or at any trial site, to discuss all their options with their health care provider, and to carefully weigh all the pros and cons in order to make a fully informed decision.

With this issue, I am also pleased to introduce myself as ACRIA’s new Executive Director. Committed to finding effective and safe treatment for HIV disease, and ultimately a cure for AIDS, I am very excited to join ACRIA. After 11 years under the skilled leadership of J Daniel Stricker, ACRIA is well-positioned to lead this battle and bring new attention to the fight against AIDS – both in treatment and HIV health literacy.

As a long-time advocate for underserved communities, working with the Coalition for the Homeless, Housing Works, and as Director of Housing Opportunities for Persons with AIDS (HOPWA) at the Postgraduate Center for Mental Health, I am especially proud to join an organization committed to HIV treatment access and educational services for marginalized populations.

I welcome your comments and insights and look forward to working with you in the fight against AIDS.

Daniel Tietz, Editor-in-Chief

Entry Inhibitors: The Ups and Downs of Drug Development

by Lynda Dee

I have been an AIDS activist since 1986 but just when I thought I’d seen it all, the seesaw phenomenon that is drug development caught me off-balance again. Entry inhibitors (EIs) have made HIV drug development an even more dangerous roller coaster ride for both companies and people with HIV. Here is one activist’s take on the history of another “promising new class” of HIV drugs.

A “Cleaner” Drug?

The story of EIs begins ten years ago, when researchers began finding people who had been exposed to HIV many times but had never been infected. The mystery was solved when, in

1996, they reported that these individuals lacked a CCR5 receptor on their T cells. Turns out that HIV attaches not only to the CD4 receptor on T cells, but also to a co-receptor: either CCR5 (R5) or CXCR4 (X4). People lacking this co-receptor weren’t getting infected, no matter how much unsafe sex they had.

This led to hopes of new HIV vaccine approaches and to a new class of drugs: EIs. These drugs were designed to “clog up” the R5 or X4 co-receptors. If an EI was effective, HIV could attach to the CD4 receptor, but it couldn’t “unlock” the cell’s coat since the co-receptor was blocked by an EI. The drugs worked in the test

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DUET: TMC 114 & 125 for Drug-Resistant HIV

People who are resistant to PIs and NNRTIs will take TMC125 (a new NNRTI) or a placebo (dummy) pill. Everyone will also take TMC114 (a new PI) with Norvir and other anti-HIV drugs. Participants must be 18 or older and have a viral load over 5,000.

TMC 114 Expanded Access Program

People who have taken anti-HIV drugs from three of the four classes of drugs (an NRTI, NNRTI and two PIs), and who have limited or no treatment options due to resistance or intolerance, will take TMC 114 (a new PI) along with other anti-HIV drugs. Participants must be 18 or older, have a CD4 count below 200 and must not be eligible for the DUET study.

IMPACT: Reyataz Resistance

People who have developed resistance to Reyataz will come in for one day of blood tests to study the I50L mutation.

Pregabalin for Peripheral Neuropathy

People with HIV who have peripheral neuropathy will take either pregabalin (Lyrica) or a placebo (dummy pill) for 3 months. Participants must be 18 or older and have had pain in their hands or feet for at least 3 months.

For the above trials, contact Dr. Douglas Mendez at 212-924-3934 ext. 126 or Dr. Yuriy Akulov at ext. 124.

TH9507 for Lipodystrophy (closed to enrollment)

People who have excess abdominal fat and who are taking anti-HIV drugs will take either TH9507 (an experimental growth hormone releasing factor) or a placebo for 26 weeks.

Maraviroc for Drug-Resistant HIV (closed to enrollment)

People who have taken anti-HIV drugs from three of the four classes of drugs will either take maraviroc (an experimental HIV attachment inhibitor) or placebo with an optimized regimen of anti-HIV drugs for 11 months.

Editor's Notes

- All material in *ACRIA Update* is presented for educational and informational purposes only, and is not intended as medical advice. All decisions regarding one's personal treatment and therapy choices should be made in consultation with a physician.
- *ACRIA Update* refers to most drugs by both their commercial and scientific names upon their first reference in an article. Thereafter in the article, they will be identified with the name by which we feel they are most commonly known, either commercial or scientific.

Entry Inhibitors *(continued from first page)*

tube, promising fewer side effects and potent viral suppression, even in people resistant to many approved HIV drugs. But as we've seen in the past, the anticipation may have far exceeded the actual event.

This new class of drugs presents many challenges with respect to safety and side effects. Initially, we were peppered with the concept that these drugs would be "cleaner" than previous drugs like protease inhibitors (PIs). My first thought was, "Where have I heard that before?" Because EIs should prevent HIV from actually entering uninfected cells, the theory was that they would lower HIV replication without affecting healthy cells.

Researchers initially suggested that EIs should be tested only in people with early HIV disease due to fears that if the R5 receptors were blocked, HIV would shift to using X4 receptors, perhaps leading to faster HIV progression. This sounded only too familiar to long-time activists. Years before, other elite researchers had told us that all new drugs should be studied in antiviral-naïve patients so we could better prove just how effective the newer drugs were. They swore we that would thwart the development of promising new drugs by studying them in people who were too sick to actually show real benefit. We were told we should forgo studying new drugs in the people who needed them the most.

Treatment activists didn't go for that line then, and we didn't this time either. We insisted that the FDA force companies to study these drugs in all patient populations before they became more widely available after FDA approval. This has resulted in another unforeseeable turn of events and a divergence of opinion between US and European activists, which I'll explain further when we discuss the specific drugs.

There were other safety issues that also needed to be addressed. Theoretically, EIs might cause immune system interactions that will result in the proliferation of other pathogens in the blood, including well-known opportunistic infections and

deadly new cancers. Resulting immune complications are of paramount concern even if these drugs are supposed to be "clean" in and of themselves.

BMS 806: Too Many Pills

The EI saga began with a compound from Bristol-Myers Squibb (BMS) that was initially further along than the rest of the pack. In test-tube studies, BMS 806 inhibited the first step in HIV entry by binding with a part of the HIV envelope, gp120. Since it bound with HIV, not a CD4 cell, it was hoped that this compound would block HIV entry regardless of whether the virus used the X4 or R5 co-receptor.

"Researchers swore that we would thwart the development of promising new drugs by studying them in people who were too sick to actually show real benefit."

In 2002, BMS was the leader in this field and claimed that BMS 806 had a tolerable safety profile and no cross-resistance to other approved HIV drugs. It was also orally bioavailable – a tablet, not an injection like Roche's Fuzeon, which causes injection site reactions in 98% of cases and costs over \$20,000 a year.

But four years later, BMS has not produced a usable version of 806. They haven't been able to solve the problem of how to get enough drug into the bloodstream without requiring an unacceptable number of pills too many times each day.

Aplaviroc: Liver Toxicity

GlaxoSmithKline (Glaxo) also had an entry inhibitor – GW873140, or aplaviroc – that it purchased from a Japanese drug company. But development was discontinued due to liver toxicity. A small number of people in early trials were seeing abnormalities in three different indicators of liver function increase simultaneously: ALT, AST and bilirubin. This phenomenon, known as Hy's Law, can predict permanent liver damage. Glaxo immediately stopped the studies, and is to be commended for acting swiftly to ensure patient safety. (Remember, these were the drugs that weren't supposed to have any side effects.) Meanwhile, another one bites the dust!

Vicriviroc: Potency Problems

Schering Plough was initially developing SCH C, another R5 attachment inhibitor. But this compound was shelved after EKGs of patients showed QT irregularities (heartbeat abnormalities). Schering decided to proceed with development of SCH D, now known as vicriviroc (VCV). Schering claimed this compound was more potent and did not cause life-threatening heart problems. As an added benefit, it was taken only once a day. In 2003, VCV had not yet been studied in the clinic but was said to offer "great promise."

Unfortunately, we once again learned the hard way that all drugs offer great promise until they are tested in people. When large numbers of people begin using new drugs, more issues are bound to develop. For example, soon after meeting with activists and telling us how rosy everything looked with VCV, Schering announced that the lowest dose in the Phase II trial was dropped after the Data Safety Monitoring Board (DSMB) saw viral load breakthroughs. Then, the DSMB (a group of experts that reviews blinded studies to ensure patient safety) recommended closing the study entirely because of viral load breakthroughs at all three doses. We still don't know why viral breakthrough occurred, but Schering is hoping that higher doses will do the trick.

It should be noted that the VCV study in
(continued on next page)

Entry Inhibitors *(continued from previous page)*

treatment-experienced patients is continuing, even though cancers have developed in five patients, including four lymphoma patients and one patient with stomach adenocarcinoma. Let's hope VCV will continue to hold its own against Sustiva and Combivir in this population, without making them sicker than they already were.

Schering is requesting FDA approval to start larger Phase III trials with higher doses of VCV, but the company may be required to go back to the drawing board with another Phase II study to find the correct dose. Restarting a Phase II study will add at least two years to VCV development. Moreover, higher doses of VCV may cause new and unforeseen side effects.

Maraviroc:

The Liver Transplant Scare

Next we have Pfizer's UK 427, now known as maraviroc (MVC). Because of all the foregoing tales of woe, MVC is further along in development than the other EIs. MVC blocks viral replication at the point of membrane fusion by preventing the gp120 viral envelope from binding to the R5 co-receptor. The really good news about this compound is that unlike VCV, MVC does not need to be boosted by Norvir, the side-effect-ridden, extremely expensive Abbott PI.

This is probably the most complicated and unclear EI story of all. Apparently, a woman in one of Pfizer's international trials needed a liver transplant after receiving MVC. This case was disclosed at a scientific conference in Europe and caused transcontinental panic. Coupled with the liver toxicity resulting from the Glaxo EI, this case made people fear that liver toxicity might be a problem with the entire class of EIs, a problem that would result in the discontinuation of all EIs.

But – you guessed it – this case is far from clear. We may never know what caused the need for this liver transplant, as many confounding factors were present. Did MVC cause the liver damage? Was it MVC or MVC plus the INH she was taking to prevent TB that caused the prob-

lem? Or was it MVC, INH, and poor medical care? Apparently, she was given INH – which is highly liver toxic – to prevent TB, without any indication that she was at risk for TB (other than the country she came from). Further, she was given Tylenol – also liver toxic – for initial symptoms and IV Tylenol after hospitalization. The patient also had hepatitis C, although her HCV viral load was undetectable. So, we have a patient who prob-

“European activists fear that not enough is known about these compounds and that patients with CD4 counts below 200 should not be exposed to the unknown risk and potentially suboptimal benefit of new drugs.”

ably had a compromised liver, receiving two drugs known to be toxic to the liver (INH and Tylenol) and an investigational drug (MVC). Who's to say for sure what actually caused the liver damage that led to the liver transplant?

What's even more concerning is that in addition to the liver transplant incident, Pfizer's DSMB recently recommended that the lowest dose of MVC + Combivir in its study in people who had never taken anti-HIV drugs be stopped because the Sustiva + Combivir arm was outperforming the MVC arm. Is this *deja vu*? Let's

hope the higher doses of MVC keep performing well against Sustiva.

It is important to note that the MVC + Combivir vs. Sustiva + Combivir study in treatment-experienced patients is continuing, with MVC holding its own against Sustiva so far. It should also be noted that Sustiva + Combivir is one of the best first-line regimens we have against HIV. But Pfizer is now very happy that the FDA forced them take our recommendation and study MVC in later-stage patients, too.

The European Conflict

Many European AIDS activists firmly believe that newer drugs like MVC should not be studied in naive patients, especially if they have a CD4 count below 200. They fear that not enough is known about these compounds and that patients below 200 should not be exposed to the unknown risk and potentially suboptimal benefit of new drugs when other, more tried-and-true regimens are available. When reviewing the protocol, many U.S. activists thought it would be better to study these drugs in all populations before they received FDA approval. We believed that most physicians would not subject their patients with CD4 counts below 200 to experimental agents when over 20 HIV drugs were readily available. Enter the previously described “perfect storm” liver transplant scenario, and yet another controversial trial design question gathered steam: is it appropriate to study new agents in people who are at risk of serious illness but who have proven treatment options remaining?

AMD 11070: The Lone X4 Inhibitor

Can we inhibit the potentially more dangerous X4 virus? AMD 3100, an X4 coreceptor inhibitor, was being studied by AnorMed, but trials were also halted due to life-threatening adverse events. AnorMed is proceeding with AMD 11070, which does not have the same dangerous toxicity profile as 3100. Unfortunately, the current AMD 11070 study (ACTG A5210) opened in November of 2004 but has still accrued only four of the required 48 patients necessary, largely because people must stay

in the hospital for 10 days. Although the protocol team continues to make amendments that should help enrollment, at this rate it won't be fully enrolled until 2030. Hopefully, the X4 shift may not be as dangerous as once anticipated because other already marketed antivirals may effectively inhibit X4 virus.

Tropism Assays

As if that weren't enough, we are far from understanding the previously mentioned, potentially dangerous shift from R5 to X4 virus. It now seems that R5 inhibition may serve merely to make already existing X4 virus more visible to currently available tests. Maybe significant amounts of dual-tropic HIV (virus that can use either the R5 or X4 receptor) were already present before initiation of EI therapy. Of course, we would know a lot more about this issue if the only approved tropism assay was better able to detect the presence of R5 and/or X4 virus.

Presently, there is only one company producing a tropism assay, Monogram Biosciences. More companies involved in assay development would undoubtedly translate into more, possibly better and less

expensive assays. But it seems that many of the funding sources have dried up as a result of the poor trial results discussed earlier. Unfortunately, the Monogram assay leaves a lot to be desired. It is very expensive – between \$800 to \$1,200 per test. It is also a very labor-intensive process that requires that a patient have a viral load over 500. And it cannot detect virus that makes up less than 10% of the viral population. This means that plenty of the more dangerous X4 virus may be present, but undetectable with the current technology.

Where does this leave EIs?

It appears we may need to reconsider the role of EIs. They may end up being merely add-on drugs, instead of the anchor drugs (like Sustiva and Kaletra) we had hoped for. Further study will describe more fully the risk/benefit ratio of these compounds. Will they have potent and sustained anti-HIV activity? If they do, the resulting benefit must be weighed against what other side effects develop and the unknown factor of their long-term effects on the immune system's other regulatory functions. Maybe these drugs will end up being added to regimens used only by treatment-experienced patients who

have burned through all other therapies and who are willing to take more risk.

But there is yet another issue. In all studies so far, we have seen substantial variation among patients in sensitivity to EIs. What factors will predict this patient variability? How many years of study will it take to sort out these strategic issues? Just when will we know how to use these drugs effectively in the real world? Is your head spinning yet?

In any event, it seems that the new integrase inhibitors being developed by Merck and Gilead Sciences may overtake EI development. Merck's MK 518 began Phase III trials in March. Although 518 needs to be taken twice daily, it does not require Norvir boosting and Merck says it is extremely effective against many types of HIV drug-resistant virus. Merck claims that this "promising" new drug will present much less risk than the EIs. Where have I heard that before?

Lynda Dee is a long-time activist and member of AIDS Action Baltimore, AIDS Treatment Activist Coalition, and Treatment Action Group.

New Drugs from Old Classes

A number of new drugs from existing classes are being studied. Here's a brief rundown of drugs that have started trials in people:

Nucleoside Analog Reverse Transcriptase Inhibitors (NRTIs):

- Amdoxovir (DAPD): Early results from an ongoing Phase II study (in people resistant to other NRTIs) showed only a modest anti-HIV effect after two weeks on the drug.
- AVX 754: active *in vitro* against HIV resistant to other NRTIs. Currently in early Phase II trials.
- Elvucitabine (ACH 126,443, L-Fd4C): active *in vitro* against HIV that is resistant to Efavirenz. Currently in Phase I trials. Also active against hepatitis B virus. It may be used once a day or perhaps even once a week.
- Racivir (PSI 5004): similar to Emtriva (FTC); active against HIV and hepatitis B virus that is resistant to Efavirenz (3TC). Currently in Phase II trials.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):

- Etravirine (TMC 125): Recent study showed effectiveness in people resistant to Sustiva and Viramune; may be very strong in people who have never taken an NNRTI. Currently in Phase II trials. Taken twice a day.
- TMC278 (DAPY): shows *in vitro* activity against NNRTI-resistant virus; in early development.

Protease Inhibitors (PIs):

- Brexanavir (GW 640385): active *in vitro* against resistant virus. In Phase II trials. Taken with Norvir.
- Darunavir (TMC 114): Phase II trial showed drug to be effective in people with multi-drug resistance – may receive FDA approval as early as this summer. Taken twice daily with Norvir (ritonavir).

Integrase Inhibitors: The Next Wave?

by Donna M. Kaminski

In 2006, the ten-year anniversary of HAART (highly active antiretroviral therapy), we have over 20 HIV medications in our arsenal. But the need for a "new wave" of HIV medications that can target new steps in HIV's life cycle remains strong. HIV can change and develop resistance to HIV medications, seriously affecting the ability of people with HIV to construct a viable treatment regimen. However, the development of new drugs that attach to different parts of HIV or CD4 cells offers hope for expanding HIV treatment choices, particularly for those whose virus has developed resistance. Integrase inhibitors are one new class of HIV medications currently being investigated.

Integrase inhibitors, like many antiretroviral medications, work by binding to one of several specific enzymes that HIV uses when copying itself. The current approved HIV drugs target and form a tight bond with HIV's reverse transcriptase and protease enzymes. Once bound to the drug, the enzyme is unavailable to anything around it, including HIV, hindering HIV's ability to make copies of itself.

In the same way, integrase inhibitors bind to integrase, the enzyme HIV uses to insert its newly made genetic material (DNA) into a CD4 cell's DNA. Their development marks an important frontier in HIV research, since integrase is one of the only enzymes that hasn't yet been successfully targeted. After ten years of attempts to design an integrase inhibitor with little success (including L-870810, zintevir, and S-1360), research presented at the 13th Conference on Retroviruses and Opportunistic Infections (CROI) finally shows two candidates, MK-518 and GS-9317, that could be the first successful integrase inhibitors.

MK-518

Of the two, Merck's drug (MK-518) is furthest along in development, and initial reports show that it is both strong at suppressing HIV and well-tolerated. It is currently being studied in a six-month trial of 167 people with HIV that is highly resistant to all three classes of antiretroviral drugs. Half of them have no active HIV drugs remaining, and 98% are resistant to all protease inhibitors. They took one of three doses (200, 400, or 600 mg) of MK-518 twice a day, or a placebo (dummy pill), along with an optimized background regimen of HIV drugs.

One of the investigators, Beatriz Grinsztejn, reported that after four months, 65-85% of the people in the trial had their

HIV viral load drop to below 400. Furthermore, between 56 and 72% of those taking MK-518 had their viral load drop below 50 – an impressive result, and quite promising for people with highly resistant virus. During this same time period, people taking the 600 mg and 400 mg doses saw their CD4 counts increase by 100 to 110 cells on average, and those on the 200 mg dose on average had a 30-cell increase. While it will be useful to see what the results look like at the end of the six-month trial, these findings show that, at least initially, MK-518 is quite effective at lowering viral load in people who have high levels of resistance to multiple HIV drugs.

“After ten years of attempts to design an integrase inhibitor with little success, research finally shows two candidates that could be the first successful integrase inhibitors.”

Understandably, this report generated enthusiasm about MK-518's prospects as a potential integrase inhibitor. Previous studies showed that other HIV drugs most likely won't interact with MK-518, and that it can be taken with or without food. While many HIV drugs use the protein CYP3A4 to get broken down in the body; MK-518 does not. This means that HIV drugs such as protease inhibitors most likely won't interact with MK-518. It's also unlikely that we'll need to add low-dose Norvir (ritonavir) to MK-518 to create simpler dosing. It also looks as if MK-518 will be able to be taken with or without food, and without any dietary restrictions.

As far as side effects go, so far they are few and mild. In Grinsztejn's study, nausea was the most commonly reported side effect (11% among those on the 600 mg dose, and 5% among those on the 400 and 200 mg doses); however, just as many people taking placebo also reported nausea. In addition, 2-10% of patients taking MK-518 reported diarrhea, fatigue, headache, or itching (pruritis). But these same side effects (with the exception of pruritis) were also reported in 2-9% of those taking placebo. Also, 8% of those on the 200 mg and 600 mg doses reported higher than normal bilirubin levels, which sometimes signal liver problems. In addition, 5% of those on the highest dose had increased amylase levels (which can signal pancreas problems).

The final results of this study are promising, but they only begin to provide the understanding we need about MK-518 in order to fully discern how useful it would be as an antiretroviral. The good news is that a larger and longer phase III study has recently opened, and will hopefully answer these questions.

GS-9137

Another integrase inhibitor, GS-9137, is being developed by Gilead. This drug is still in early development, but researcher Edwin de Jesus presented the first study in humans. Forty people, half of whom had never taken HIV medications, with viral loads between 10,000 and 300,000 and CD4 counts of at least 200, were in the study. They stopped all antiretrovirals prior to the start of the study and then took one of five doses of GS-9137, either once or twice a day, or a placebo. One group also took Norvir, but no other antiretrovirals were given.

After ten days, there was an overall reduction in viral load of 1.44 to 2 logs among the various doses, which means that, on average, people who had a viral load of 100,000 would have dropped to 3,571-1,000 after 10 days. Those on placebo, on the other hand, reported only a 0.26 log drop, which would mean a much smaller drop, down to 50,000 copies.

While this shows that GS-9137 may have a strong antiviral effect, the study's main purpose was to look at safety and side effects. Overall, GS-9137 was well tolerated in this short study and no one withdrew due to side effects. The side effects reported included fatigue, diarrhea, headache, and nausea, and were mild to moderate. Individuals taking 400 mg twice-daily also reported an increase in triglyceride levels, and those taking 50 mg boosted with Norvir and those on placebo reported an increase in amylase levels. These lab abnormalities were moderate to severe but are not conclusive due to the small number of people in the study.

Unlike MK-518, GS-9137 is broken down through the CYP3A pathway in the liver. This means that it is more likely to interact with other HIV drugs; either the dose of GS-9137 or the other

drugs might need to be adjusted. For example, levels of GS-9137 have already been shown to rise 20 times higher when taken with Norvir, which shows there may be some benefit to taking GS-9137 with low-dose Norvir. Also, in order to be broken down properly, GS-9137 needs to be taken with food.

In addition, it looks as though GS-9137 stays in the body longer than many other HIV drugs (as long as nine hours), which promises less frequent dosing. At this early stage, it looks like there shouldn't be any cross-resistance between GS-9137 and MK-518, which means that if someone's virus stops responding to one of the drugs, the other one might still work. But these preliminary findings tell us little about how well GS-9137 will work or its safety in larger groups of people. A larger and longer phase II study is set to open in May and should provide us with many more answers.

Looking Ahead

The presentation of these studies at the conference made many people wonder if MK-518 or GS-9137 could finally be the first integrase inhibitors to succeed, after so many others in this class have failed. MK-518 seems to work in people who have highly resistant virus, and GS-9137 looks safe overall. By now, you may also be wondering: Could they be part of the next new wave of HIV drugs? The bottom line is that we simply know too little about either drug at this point to say, nor will we for some time. But we certainly can keep our eyes open for what's on the horizon, be it integrase inhibitors or other HIV drugs.

Donna M. Kaminski is the former Associate Director of Treatment Education at ACRIA and currently a first-year medical student.

ACRIA Study of HIV Health Literacy Needs

ACRIA is conducting a survey, sponsored by NYC Community of Color HIV/AIDS Coalition, to study the need for HIV health literacy education among people with HIV in NYC. The survey is being conducted with the help of several community-based agencies.

If you are HIV positive and interested in participating, please stop by ACRIA on May 2, 3, or 4 between 11 a.m. and 4 p.m. to complete a survey. No appointment is necessary.

The questionnaire is anonymous and takes 15 to 20 minutes to complete. Snacks are available, but the study provides no compensation or Metrocards.

ACRIA is located at 230 West 38th St between 7th and 8th Ave. in Manhattan. Our offices are on the 17th floor. If you are interested, feel free to walk in May 2 - 4.

Call Nicola at 212-924-3934 x128 for more info.

Treatment Interruptions: SMART or Stupid?

By *Tim Horn and Mark Milano*

Ten years ago, when HAART (highly active antiretroviral therapy) made its debut, the theory behind using a combination of HIV drugs seemed easy enough to understand. Preliminary data suggested that HIV could be cured – “eradicated,” as experts were prone to say – if people on HAART could simply keep their viral loads undetectable for a little more than two years. Two years of treatment? No problem.

Unfortunately, within a few years several studies confirmed that even the most powerful combinations of the available HIV drugs were unable to completely stop HIV from reproducing in the body. As a result, the hope of eradicating HIV gave way to a much more sobering reality: once someone needs HIV drug treatment, that person will likely need to stay on therapy for the rest of his or her life.

Ten years later, real-world experience has shown how difficult it can be for some to stay on HAART for very long periods of time. HIV meds can cause a number of long-term side effects, including liver problems, body-shape changes, and increased lipids (such as cholesterol and triglycerides). Because of this, researchers soon began looking into a treatment technique called “structured treatment interruptions,” or STIs for short.

STIs have been studied in a number of different ways. They have been tried in people who achieve high CD4 counts after many months or years on treatment; in people experiencing long-term side effects of HIV meds; in people with HIV drug resistance (with the hope that stopping therapy might help their virus switch to a strain that is sensitive to available drugs); and to boost the immune system (using STIs to boost the activity of the HIV-specific CD4 cells that can help control HIV). Results from these studies, however, have been mixed.

Another approach that has been explored is the possibility of treating

HIV like other chronic diseases: starting therapy when the immune system shows signs of damage or when a patient experiences symptoms of HIV disease, and stopping it when their health improves. This STI approach was explored in the SMART (Strategies for Management of Antiretroviral Therapy) study, a large (6,000 people) and long (almost 9 years) clinical trial.

“People with HIV were taken by surprise when it was announced that the SMART study was being stopped after only 14 months, due to a high rate of disease progression in those assigned to treatment interruptions.”

Not expecting results for several years, many healthcare providers, advocates, and people living with HIV were taken by surprise when it was announced in January that SMART was being stopped after only 14 months, due to a high rate of disease progression in those who were assigned to STIs. But do the SMART results signal a death knell for this approach and other types of STIs? Let’s take a closer look.

SMART enrolled people with CD4 counts above 350, who were either on treatment or who had not yet started therapy. They

were randomized to one of two groups: a continuous treatment (CT) group that did not stop HIV treatment, or an STI group that stopped treatment until the CD4 count fell below 250, restarted when the CD4 count rose above 350, stopped again until it fell below 250, and so on.

The researchers conducting SMART hoped that repeated STIs would allow people to maintain CD4 counts that would be high enough to keep them healthy while at the same time reducing the amount of time on treatment and lowering the risk of side effects.

On January 10th, when the study’s DSMB (Data Safety and Monitoring Board) recommended halting SMART, the study had enrolled 5,472 patients. While the study is technically still being conducted, no new patients are being enrolled and patients in the STI group – especially those who had tried and failed other anti-HIV drugs in the past – have been advised to restart treatment and to remain on therapy.

Dr. Wafaa El-Sadr, Chief of the Infectious Disease Division at Harlem Hospital in New York and a leading SMART researcher, presented the data at the recent Retrovirus conference in Denver. She reported that there were 164 “events” during the 14 weeks of study follow up. These events were defined as either death or the development of a serious AIDS-related condition or another serious complication (such as a potential side effect).

There were 47 events in the CT group, and 117 events in the STI group. In other words, people on STIs had 2 1/2 times the risk of a serious event. 0.6% of patients in the CT group progressed to AIDS, compared to 0.9% of patients in the STI group. (Esophageal candidiasis was the most common AIDS-related sign of disease progression among people on STIs.) And 0.9% of patients in the CT group died, compared to 1.7% of people in the STI group.

Cause of death	STI	CT
AIDS	3	1
Hepatic	3	4
Pancreatic/GI	1	0
Cancer	8	5
Cardiovascular	13	10
Other	9	2
Unknown	11	2

The causes of death in the study were confusing. Only a small number of deaths were due to AIDS-defining conditions. And while there were slightly more deaths in the STI group from some causes (as seen in the table above), the real difference came in the “Other” and “Unknown” categories. “Other” refers to deaths stemming from violence or accidents. But until we know what caused the deaths in the “Unknown” category, it will be hard to draw final conclusions from the study.

Another surprise: the SMART researchers were hoping that STIs would lead to fewer complications that can be caused by HIV treatment, such as heart attacks, stroke, coronary artery disease, kidney problems, and liver damage. But they actually found more complications in the STI group. According to Dr. El-Sadr’s report, 2.1% of patients on STIs experienced a serious complication, compared to 1.4% of patients in the CT group.

Many STI studies have reported that the lower a person’s CD4 “nadir” (the lowest their CD4 count has ever been), the more likely it is that someone will progress while attempting an STI. This was not the case in SMART – people with both low and high CD4 nadirs experienced “events” during the study. What’s more, patients who had viral loads below 400 at

the time they stopped therapy were more likely to have an event than those who stopped therapy with higher viral loads. (Perhaps the inflammation associated with viral load rebounds after a long period of suppression may be harmful, but this is only conjecture.)

So SMART’s conclusion, based on the data presented so far, is clear but limited: STIs using the approach of stopping treatment when CD4 counts are higher than 350 and restarting when it drops below 250 are inferior to continuous treatment – the current standard-of-care.

But questions were raised at the conference. A sizeable number of people had a history of an AIDS diagnosis (24%), and many (95%) had tried and failed other treatments in the past. Would a study involving people who had a healthier history and less resistance to anti-HIV treatment yield different results? Were the stop and start points (250 and 350) too close together? Could the time since the CD4 nadir have an effect on the safety of an STI?

Making sense of the SMART data will be tricky. Similar trials presented at the conference showed conflicting results. For example, in the STACCATO trial, a similar study reported at the conference, people doing STIs who restarted treatment at a higher CD4 count—350, compared to SMART’s 250 – were no more likely to die or experience an AIDS-related complication, compared to those who remained on continuous therapy. But another study reported at the conference (the TRIVACAN study), mirrored the results of SMART. It, too, used a CD4 count of 250 to restart patients on treatment.

While SMART, TRIVACAN, and STACCATO all used patients’ CD4 counts to determine when treatment should be stopped or restarted, other STI approaches have been tried, including those using weekly and monthly timeframes instead. For example, the Italian ISS PART study compared 137 people on continuous therapy to 136 people doing increasingly long STIs (of one, two and three

months, each followed by three months on treatment), and had positive results: while the STI group had a slight drop in CD4 counts after two years (a decrease of 28 cells compared to no decrease in the CT group), 91% of the STI group and 92% of the CT group had viral loads below 400.

The French WINDOWS study compared CT to a two-months-on, two-months-off STI approach in 403 people. After 21 months, there were no AIDS-defining events in either group. While more people in the CT group had CD4 counts above 450 (92% compared to 75% of people doing repeated STIs), the development of resistance was similar in both arms (17 in the STI group and 14 in the CT group).

So perhaps the only real lesson from the SMART study is that using CD4 counts of 350 and 250 to repeatedly stop and restart therapy may not be such a good idea, especially in people with a history of advanced disease. The STACCATO study suggests that episodic treatment, using CD4 counts as a guide, may be possible if a higher CD4 count is used to restart treatment. And the ISS PART and WINDOWS studies suggest that structured weekly or monthly timetables for stopping and restarting treatment may also be worthwhile.

In the end, as often happens with studies that are designed to give a “final answer” to a major question, the conclusions of these studies yield even more questions than answers. For the near future, the message for people with HIV who want to take a break from their meds remains the same: STIs are risky at best, and should not be attempted without a careful evaluation of the risk and benefits, and certainly not without the guidance of an HIV expert or within a clinical trial.

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Mark Milano is a longtime HIV treatment activist and Editor of ACRIA Update.

(In the Fall of 2003, ACRIA Update's Drugs! Drugs! Drugs! issue gave an overview of all the FDA-approved HIV drugs. Since that issue, one new HIV drug has been approved. We present it here for those wishing to add it to that issue, which is available online at acria.org.)

Aptivus is the latest protease inhibitor (PI) to receive FDA approval. For a while, it seemed like dosing problems might derail its development, but the drug's benefits for people with PI-resistant HIV led to a narrowly defined approval in June of 2005.

Background

Aptivus is the first non-peptide-based PI to receive FDA approval. (Darunavir, also known as TMC 114, may be the second, this summer.) Previous agents (U-96988 and U-103017) had failed in the early 1990s, but Pharmacia & Upjohn (P&J) generated considerable buzz in June of 1999 when the company reported exciting *in vitro* (test tube) results of its new compound PNU-140690. Tests showed that 96 of 107 strains of HIV that were highly resistant to currently available PIs were fully sensitive to this new PI.

The effectiveness of this new PI against resistant HIV stemmed from its molecular structure. Whereas all the approved PIs imitated the peptide target of HIV protease, this new compound worked differently. Its structure allowed the drug to bind uniquely with HIV's protease enzyme, so it was not as affected by prior PI resistance mutations. For the many people who had burned through all the older PIs, this offered hope of an effective new drug in the treatment arsenal.

But in human trials, dosing was a problem. In order to achieve adequate drug levels in the body, early studies required eight pills to be taken three times a day with a big meal. At a time when companies were looking for once-a-day drugs with low pill counts, P&J apparently decided that such dosing would limit the drug's market, and in 2000 Boehringer Ingelheim (BI) acquired the rights to develop the drug, now called tipranavir.

Early Studies

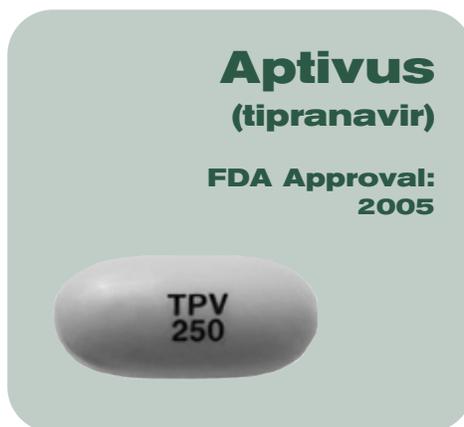
BI began Phase II studies of tipranavir with P&J's hard-fill capsule, but soon reformulated the drug as a soft-gel capsule. This meant essentially going back to square one with the drug, and activists wondered if the right dose of this drug would ever be found.

BI's first study (BI 1182.2) was problematic, since it started with the hard-fill capsules and switched to the soft-gel version mid-study. In the study, 41 people took either 1200 mg or 2400 mg of tipranavir twice a day along with Sustiva and two NRTIs. Surprisingly, more people on the lower dose achieved a viral load

below 50 than those on the higher dose (68% v. 41%). The probable explanation was poor adherence due to the hard fill capsules used at first.

So, BI tried once again to find the elusive best dose of tipranavir, this time using the emerging strategy of boosting PI blood levels with low doses of Norvir (ritonavir). Another dosing study (BI 1182.52) looked at three different twice-daily doses, boosted with Norvir. Each participant took tipranavir with an optimized background regimen based on resistance testing and their treatment history. Over 90% of participants had 10 or more PI mutations, and all had used at least two PIs.

After six months, 40% of people taking 500 mg of tipranavir with 200 mg of Norvir twice a day saw a one log (90%) decrease in their viral load. Since those taking a higher dose (750 mg) had almost the same result (45%), BI decided the 500 mg dose was better. Unfortunately, this meant taking 400 mg of Norvir a day (most boosted PIs use 100 or 200 mg of Norvir a day), leading to more of the side effects that drug is famous for – 31% of people reported diarrhea and nausea. (Aptivus lowers levels of Norvir in the body, or these numbers might have been worse.) At this dose, 7% of people had elevated liver enzymes, 11% elevated bilirubin, and 27% elevated triglycerides.



RESIST

So now we finally had a dose – the question was: would the drug work? The pivotal trials to provide the answer were the RESIST I & II studies (Randomized Evaluation of Strategic Intervention in Multi-Drug Resistant Patients with Tipranavir). A total of 1,483 people were enrolled in North America, Australia, Europe and Latin America. People who had used an average of 12 anti-HIV drugs and who had resistance to at least two PIs took either tipranavir with Norvir or an approved PI with Norvir, along with other anti-HIV drugs chosen after resistance testing.

Aptivus was approved based on 6 months of data, but we now have results for 11 months: 30.4% of people taking Aptivus achieved viral loads below 400, compared to 13.8% taking another PI. While Aptivus did more than twice as well as other PIs, the low numbers emphasize the need for at least two active agents in a regimen. Twice the number of people who also used Fuzeon (enfuvirtide) – about 25% of people in the RESIST studies – achieved a one log (90%) decrease in viral load. (Fuzeon was often the only other drug to which this group was not resistant, and was especially effective in people with viral loads above 100,000, CD4 counts below 75, prior use of more than 13 anti-HIV drugs and more than two resistance mutations.) Nevertheless, anyone who had two or more active drugs in their background regimen did better in these studies than those who

didn't. Bottom line: Aptivus works against PI-resistant HIV, but the effect may not last if there are no other active drugs in your regimen.

Since everyone in the RESIST studies was taking a Norvir-boosted PI, it's useful to compare side effect rates, since that gives an idea of which side effects were caused by Aptivus and which by Norvir. Stomach pain, vomiting, fatigue, headache and rash were reported about as often in people taking Aptivus or another PI. Diarrhea was reported more often in those on Aptivus (10.9% compared to 9.4%) as was nausea (6.7% compared to 4.6%). But the most significant concerns were with liver function tests, leading to the warning that is included in the drug's label (see Side Effects, below).

Approval for Resistant HIV

In June of 2005, the FDA granted accelerated approval to Aptivus for people who are "highly treatment-experienced or have HIV . . . resistant to multiple protease inhibitors." The FDA advisory panel asked for more info on Aptivus in women, children, people with hepatitis B or C or other liver complications, and in people who have not taken anti-HIV drugs. They also asked for more studies of drug interactions and of metabolic and body shape changes.

Activists were once again disappointed with Aptivus' price: over \$13,000 a year wholesale, making it the highest-priced PI on the market (other than full-dose Norvir, which is virtually never used).

Aptivus as a First-line Drug?

To study Aptivus in people who have never taken anti-HIV drugs, BI launched a study comparing two doses of boosted Aptivus to Kaletra (BI 1182.33). But after 11 months, the study's DSMB (Data Safety Monitoring Board) closed the higher-dose Aptivus arm. Liver enzyme elevations were reported in those taking 500mg of Aptivus with 200 mg of Norvir twice a day (the dose approved for those who are resistant to PIs). The study continues to look at a dose of 500 mg Aptivus with 100 mg Norvir. More reports on this study (BI 1182.33) will follow, but at the present time Aptivus is not recommended as a first-line therapy.

Side Effects

Many of the most common side effects (diarrhea, nausea, vomiting and stomach cramps) reported in Aptivus trials may be due to the amount of Norvir that must be taken. Also, Aptivus contains sulfa, which can cause rashes and sensitivity to sunlight, so people who are allergic to sulfa drugs should use it only with caution. Skin rash has been reported in both men (8-10%) and women (14%), especially in women who are taking birth control pills or estrogen.

Aptivus' label says that the drug "has been associated with severe liver disease, including some deaths." It recommends that liver function tests should be done before starting Aptivus and "frequently" thereafter. It also advises caution when Aptivus is used by people with elevated liver enzymes

or chronic liver diseases like hepatitis B or C, and recommends it not be given to patients with moderate to severe liver disease.

People taking Aptivus are urged to check their cholesterol and triglycerides regularly and to be on the lookout for body shape changes. As with other PIs, Aptivus may worsen or cause diabetes, and people with hemophilia may experience increased bleeding.

Interactions

When Aptivus is taken with Norvir the P450 pathway in the liver is inhibited, which may raise the level of other drugs in the body. Many drugs may need to have their dose adjusted, but some drugs should not be taken with Aptivus, including certain antiarrhythmics, antihistamines, ergot derivatives, rifampin, St. John's wort and others. Be sure your doctor knows every medication you are taking (including drugs you buy without a prescription), before you start Aptivus.

When to consider it

U.S. treatment guidelines recommend Aptivus only for people with multi-drug HIV resistance. It is not recommended for treatment-naïve patients, due to the lack of clinical trial data.

Good to Know

- Keep Aptivus in a refrigerator until the bottle is opened. After opening, it can be stored at room temperature for up to 60 days.
- Videx should be taken 2 hours before or after Aptivus.
- Aptivus lowers blood levels of methadone, so people on methadone maintenance should ask their doctor if their methadone dose should be raised.
- One study showed that Aptivus lowers levels of etravirine (TMC-125), an experimental NNRTI, so use caution if combining these two drugs.
- Some people who have diarrhea from Aptivus have found that taking Immodium before dosing helps.

Pregnancy

Aptivus is classified by the FDA as a pregnancy category C drug. There have been no studies of Aptivus in pregnant women, so it should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Dose

Aptivus comes in 250 mg soft gel capsules. The dose is two capsules twice a day with 200 mg of Norvir (two 100 mg capsules). Aptivus should be taken with food to increase drug levels in the body.

Manufacturer: Boehringer Ingelheim

Patient Assistance Program: Phone number 1-800-556-8317

Personal Perspective: Resisting Resistance

by Matt Sharp

In a little over four months I will turn fifty. When I was diagnosed with HIV in 1988 I never dreamed I'd reach forty. I've survived a long battle with HIV, and it has not been easy. It's taken a concentrated and impassioned effort to gain every piece of knowledge I could in order to stay ahead of this deadly virus, one that has a basic survival instinct not unlike my own.

HIV drugs have changed the course of the epidemic in a relatively short time and have played a huge role in my survival. In fact, my treatment history reflects the progress and pitfalls of AIDS research. Each step along the way I was as aggressive as possible in my treatment decisions. Over the past 18 years my virus first became resistant, then highly resistant, and now what we call "multi-drug resistant" (MDR). Doctors use the same terminology in tuberculosis – usually signifying a serious condition, one that is difficult if not impossible to treat. In HIV, the condition is problematic not only because it becomes difficult to treat, but because MDR HIV can be transmitted to other people.

What I didn't realize when I began HIV treatment was that I was creating a recipe for disaster. The correct use of anti-HIV drugs had to be learned over time, and even though I was fortunate enough to gain access to new drugs almost as soon as they were discovered, I used them incorrectly. Each time I added a new drug to another older medication I was creating a more mutated virus. But, I was doing what anyone in my situation would do in order to survive.

For someone with MDR HIV, finding a new treatment today is just as complex as it ever was – and for me, finding an effective drug combination has been a roller coaster of decision-making with considerable frustration. In some ways it's been like a long war waged against improbable foes. I have had to consult with many doctors, haggle with drug companies, sustain risk through several clinical trials, and even get arrested in actions of civil disobedience, all to get the drugs that have kept me alive.

Most drug studies offer me only what is known as monotherapy, since they provide only one new drug in addition to the backbone of drugs I am already resistant to. It's been the bane of my existence since the early days of my HIV treatment: trying to find two active drugs to work against my crafty and persistent virus. We know now that at least two active drugs are needed for the greatest control over HIV replication. But I learned this too late.

I first began treatment back in 1989 with AZT, the cause célèbre of AIDS protests on Wall Street and at the FDA. I was one of many who started using it as monotherapy, thus starting my resistance cycle and mistaken treatment course of *sequential* monotherapy. But back then, it was all we had and we all demanded AZT.

After using AZT for several months I gained access to ddC (later approved as Hivid) from an AIDS buyers club (before it was available by prescription) and began my first dual regimen, not knowing that I was getting little, if any, benefit from ddC. I probably had already developed resistance to AZT, allowing

mutations to occur and beginning my ride on the resistance roller coaster. Shortly after this, I developed my first opportunistic infection: extrapulmonary tuberculosis. I was scared to death and afraid new HIV drugs would never materialize.

I was successfully treated for tuberculosis and moved to San Francisco in order to be connected to cutting edge care and treatment. Over the next few years I tried a lot of complementary therapies and began switching to new drugs as they became available. I took Videx and then Zerit, adding each of them to whatever I was taking. So essentially I was building new mutations and using only one effective drug at a time. This went on for several years as I slowly watched my CD4 count drop.

I was one of the first people to gain access to Rescriptor (delavirdine), the first of the drug class called NNRTIs. But this turned out to be another big mistake. Later drugs in this class, Sustiva and Viramune, would be more potent and easier to take, but I needed Rescriptor then. What we didn't know at the time is that the drugs in the NNRTI class would be highly cross-resistant to each other. If you develop resistance to one, you blow the whole class. And I did.

I became very angry and frustrated at this time, and joined ACT UP, the AIDS activist organization. Many of us who needed new drugs planned very sophisticated actions targeting drug companies, the government, and sometimes even hospitals and medical institutions. Getting arrested appeased our anger by bucking the system and making some sort of stand against the status quo. As far as I was concerned the government and research institutions could never move fast enough when everyone was dying around you. We felt an incredible bonding as brothers and sisters fighting a war together to save our own lives.

By 1994 HIV was having an effect on my health. I was wasting (losing over 20 pounds), and beginning to develop other symptoms. I was afraid. Wasting zaps your energy, drains your confidence in surviving, and damages your self esteem. Skull-like faces and "AZT butt" (severe loss of the buttock muscles) were noticeable everywhere in the Castro district of San Francisco. One prominent doctor I was seeing at the time told me that I had no more options, that there was "nothing he could do" for me and my treatment situation. I fired him that day, not willing to tolerate his apathetic approach. I knew that HIV wasn't going to do me in . . . just yet.

A study of human growth hormone saved my life, despite the fact that I received the placebo for the first part of the trial. I regained my weight and enrolled in a study of the first protease inhibitor, Invirase (saquinavir). The background drugs in this study were AZT and ddC – two drugs I had already used. So with Invirase as the only active drug in the regimen, I was once again taking virtual monotherapy. I had a lot of time to think about my health and my treatment situation as I made the hour-long drive to Stanford for each study visit. I once again found myself needing a new drug and entered a study of Crixivan. But it soon failed and my CD4 count slumped.

I had learned about research and the clinical trials process through my actual experience in trials and as a member of ACT UP Golden Gate. A group of us held an immune-based therapies “breakfast club” on Saturday mornings where we would pore over the latest journal articles and hear from graduate students and researchers from Stanford and UCSF. It led me to consider my treatment course a little differently. Up to this point every drug I had tried had failed and I realized I needed something to boost my weakened immune system.

So I joined a very progressive thymus transplantation study in hopes of restoring some thymus function, which plays an important role in the immune system. I was flown across the country to Vermont and underwent an overnight hospital stay as thymus tissue was transplanted to my abdomen. The thymus tissue was not rejected by my weakened immune system, but my CD4 count continued its slow decline. Still, I felt amazingly empowered with a renewed sense of living by participating in cutting-edge research.

For the next several years I remarkably maintained my health status while HIV research slowed. I tried other new protease inhibitors as they became available and began “recycling” my medications, reusing past drugs I was most certainly resistant to. I was technically on HAART (highly active antiretroviral therapy) but it would probably best have been described as “PAART,” since it was only *partially* active for me.

In 2002 I enrolled in a trial of the first fusion inhibitor, T-20 (Fuzeon), after nagging investigators and the companies developing the drug (Roche and Trimeris) to get the study started. I was aggressive with the investigators as I knew this was a last chance of sorts, but my bad luck landed me into the arm that did not receive Fuzeon. Fortunately, the design of the study enabled me to receive Fuzeon after 24 weeks. After I started the drug my viral load went undetectable for the first time ever – for just one week. I must admit I was thrilled yet skeptical. Since I knew I was resistant to my background regimen, Fuzeon was working alone and it was only a short time before my virus quickly developed resistance.

I still take Fuzeon, along with the newest protease inhibitor, Aptivus. These drugs plus Truvada have enabled me to stay relatively healthy, with the lowest viral load I ever had. Unfortunately, my CD4 count has dropped below 100. For me, all good things in HIV seem to end, so I now am seeking yet another new drug.

Recently, my options have gotten better thanks to a resurgence in HIV drug development. Several new drug classes are showing promise. And for the first time ever, a clinical trial is looking at two new drugs at the same time. The DUET study (see box on page 15) is looking at a combination of a new pro-

tease inhibitor (TMC 114) and an NNRTI (TMC-125) that are hopefully not cross-resistant to older drugs.

I was ready to jump into the DUET study and even screened for it. But then I met with several researchers and my doctor, and I realized that if I entered the trial, I would run the risk of getting the new protease inhibitor alone, since the trial randomized people into getting either one new active agent or two. They also felt that I most likely wouldn't get much bang out of the NNRTI anyway.

In addition, there are suddenly two very new drug classes on the horizon: integrase inhibitors and attachment inhibitors. This would afford me the option of adding them to TMC 114, and having two new drugs! But once again, because of all the

drugs I have taken, the design of the integrase inhibitor studies will not allow me to have more than two new drugs that my virus has never seen.

So I've decided not to enroll in the DUET trial and will also forego the integrase study. I am in a holding pattern, buying time and waiting until I can access the integrase inhibitor through an early access program. By that time TMC 114 will hopefully be in the pharmacy and I'll have two new active agents. It's a tenuous position to be in, but I have little choice. I'm keeping my fingers crossed that I can maintain my health until then.

Hopefully, people starting HIV treatment today will not need to go through what I did, ending up with MDR virus and few options. The prospects are

much better for choosing a regimen out of over 20 drugs that will be strong, safe and long-lasting. I think people with MDR virus should hold on as long as they can until they can gain access to at least two new drugs. Possibilities will open up for people who can wait. Sadly, there are those who can't.

It takes a lot of knowledge to follow what is happening to this tricky little virus called HIV. But people must be persistent and *demand* what they need. They should work closely with an experienced HIV doctor and know all their options. It can be done. I truly believe I am alive today not because of the mistakes I made in treatment choices, but because I was resilient, I fought back and was informed enough to buy time.

Survival can be a desperate thing. If you were stranded on a desert island, you would do whatever you had to stay alive. I think it is no different living with MDR HIV. Today, due to research breakthroughs, drug development, determination, patience, and awareness, a longer life with HIV is attainable. Maybe HIV finally is a chronic manageable disease.

Matt Sharp is Director of Treatment Education at TPAN in Chicago.

“One prominent doctor I was seeing told me that I had no more options, that there was ‘nothing he could do’ for me. I fired him that day...”

Virtual Monotherapy: Can It Be Avoided?

by Bob Munk

Twenty years ago, participating in a clinical trial was usually the only way to access an experimental HIV drug. Doctors who kept up with new developments worked hard to get their patients on drugs as soon as they became available. Unfortunately, many doctors and patients ended up adding one new drug at a time. We soon learned – painfully for many patients – that this type of “sequential monotherapy” usually has only short-term benefits. And it has the primary effect of burning through all available antiviral drugs, helping the virus accumulate additional mutations that reduce the efficacy of any future regimen.

The official Department of Health and Human Services Guidelines recognize the importance of having more than one active drug in a treatment regimen. The current version states:

- Use the [patient’s] treatment history and past and current resistance test results to identify active agents (preferably at least two fully active agents) to design a new regimen. A fully active agent is one likely to demonstrate antiretroviral activity on the basis of both the treatment history and susceptibility on drug-resistance testing.
- If at least two fully active agents cannot be identified, consider pharmacokinetic enhancement of protease inhibitors with Norvir (ritonavir) and/or re-using other prior antiretroviral agents to provide partial antiretroviral activity.
- Adding a drug with activity against drug-resistant virus (e.g. a potent Norvir-boosted PI) and a drug with a new mechanism of action (e.g. HIV entry inhibitor) to an optimized background antiretroviral regimen can provide significant antiretroviral activity.
- ***In general, one active drug should not be added to a failing regimen because drug resistance is likely to develop quickly. However, in patients with advanced HIV disease (e.g. CD4 <100) and higher risk of clinical progression, adding one active agent (with an optimized background regimen) may provide clinical benefits and should be considered.*** (Emphasis added.)

In 2006, we’re in relatively good position in terms of the drug pipeline. There are promising new agents, including some that appear to be effective against HIV that is resistant to existing drugs. And drugs are showing up in new classes: attachment and fusion inhibitors, integrase inhibitors, and maturation inhibitors. A new class of drugs carries the strong hope of a lack of cross-resistance with older classes of drugs – an extra boost to its ability to fight HIV. And yet, many patients are still risking their future treatment options by participating in clinical trials where they may only receive one new, active agent to add to their failing treatment regimen. What factors contribute to this situation? Why are people with HIV putting themselves at risk?

Clinical Trial Design

The FDA has long been aware of the risks of monotherapy in testing new drugs. In 1999 they wrote to manufacturers indicating that more than one investigational agent could be used in the same clinical trial. The FDA was very supportive of “factorial

designs” where more than one agent at a time could be studied. For example, the following is an example of a factorial design (Note: OBR means “optimized background regimen,” or the best combo that can be put together with existing drugs.)

- OBR plus new drug A
- OBR plus new drug B
- OBR plus new drugs A & B
- OBR alone

But unless your OBR includes at least one “active” agent – a drug to which your virus is not yet highly resistant – then the only arm that doesn’t expose you to monotherapy is OBR plus A + B. And of course, the whole point of a randomized trial is that you can’t choose which arm you get into.

The Lessons of Fuzeon and Aptivus

Two recent drug approvals were supported by large clinical trials that highlighted the benefits of having more than one active drug available.

The key clinical trials supporting the approval of Fuzeon (enfuvirtide) were the TORO trials. These trials generally studied a regimen that included a boosted protease inhibitor, with or without Fuzeon. When people in the TORO studies were given phenotype tests, one study found that people with 3 to 4 active drugs had an average viral load drop of 2.3 logs (99.5%) after 6 months – an impressive result. But those who had only one other drug available achieved only a 0.2 log drop (37%). The TORO studies showed that Fuzeon works best in people who have two other active HIV drugs available, and some ADAP programs require this before they will pay for Fuzeon, the most expensive HIV drug yet approved.

The newest protease inhibitor to be approved is Aptivus (see article on page 10). An analysis of the RESIST clinical trials provided clear support for the benefits of additional active drugs in the background regimen: Almost 55% of people taking Aptivus had a treatment response if they had 3 or more active drugs available. But this number dropped to 46% when only two other drugs were available, 37% with one other drug available, and 13% with no other active drugs.

The TORO and RESIST trials clearly support the value of active agents in the treatment regimen, but they also leave open a key question: the role of a new class of drug. In both sets of trials, patients who took Fuzeon did better. Was this because it was “one more active agent” or because it was a drug in a totally new class? Would another fusion inhibitor (of course, there aren’t any right now) or a drug in one of the other classes being developed (attachment inhibitors, integrase inhibitors, maturation inhibitors) have the same benefits? We won’t know the answers to these questions until some of these newer drugs are tested.

Research vs. Treatment

That puts us squarely in the middle of the dilemma of how to test new drugs. From the manufacturer’s point of view, the goal of a clinical trial is to provide key data to achieve FDA approval. The

best way to do this is to show higher response rates with their new drug than without it. But this often conflicts with the best way to optimize treatment for an individual patient.

So – what restrictions should be put on patients entering clinical trials to protect them against the risks of getting only one active drug? Should more than one experimental drug be tested in a single clinical trial? From a manufacturer’s point of view, combining experimental drugs in a trial design is challenging and risky. What about legal issues? Will the manufacturer of the other new drug cooperate? Have interaction studies been done between the new drugs, and with existing drugs? Are they safe for people with kidney problems or liver impairment (such as with hepatitis B or C)? And when the trial is over, will anyone be able to sort out the contribution of Drug A versus Drug B to treatment success?

Of course, from a patient’s point of view, allowing more than one experimental agent in a trial increases the possibility of constructing a regimen with active agents, raising the chance that the regimen that will control HIV, and avoiding real or “virtual” monotherapy.

It’s also been common for clinical trials of new drugs to include an initial period of monotherapy. The benefit is being able to see the impact of the new drug by itself. The risk is that HIV will quickly develop resistance and the new drug will become useless.

Asking the Right Questions

If you’re considering participating in a clinical trial, talk with your doctor about the following: Do we have current resistance testing results for me? If not, does it make sense to get them done now? What active drugs do I still have? Which approved medications still have a chance to contribute to control of HIV? (Remember that resistance is not “all or nothing” – you may get some benefit from drugs that show partial resistance.)

What clinical trials are available for new drugs? What phase are these trials? How much is known about the drugs being studied? What are the treatment arms in the clinical trial? Would any of them expose me to monotherapy, real or virtual? Would any of them expose me to untested dosages? What are the anticipated side effects? Is there any other way to access experimental drugs? Are there expanded access or open-label safety studies that could provide access?

Informed consent is a process intended to protect people who enter clinical trials. There are always some risks, which must be weighed against the potential benefit. Unfortunately, the clinical trials system can be slanted toward the completion of the trial, and informed consent can sometimes be less thorough than is needed. Before entering any clinical trial, it’s important to check it out with your healthcare provider, and to look for info from other sources, like an AIDS treatment organization or other people with HIV.

Where Do We Go From Here?

Clinical trials are not done to provide optimal care to trial participants. They are done to answer specific research questions about the effectiveness and safety of new drugs. On the other hand, clinical trials have always been a way for people with HIV to gain access to these new drugs. Unfortunately, most manufacturers

Options for People with Multi-Drug Resistance

Activists have long pushed for clinical trials that combine two new drugs for people who have no active agents, and one company, Tibotec, has recently begun the first such trials, of a protease inhibitor, darunavir (TMC 114), and an NNRTI, etravirine (TMC 125).

The DUET studies allow patients to take both of these drugs, although people will be randomized to receive etravirine or placebo. So there still is a 50% chance of receiving virtual monotherapy if you have no other active drugs available. (People randomized to receive only darunavir can add etravirine after 6 months if their viral load is not controlled.)

If your genotype test shows that your HIV is resistant to most approved anti-HIV drugs and you and your health care provider feel you must change your regimen, here are some options. (Not everyone who is resistant to their meds needs to switch; there may be good reasons not to.)

- Get a phenotype test to find out exactly what medications you have resistance to. Your doctor may also take into consideration your treatment history to determine Fuzeon resistance and the potential for archived resistance.
- If you have at least one active drug available, talk to your doctor about the DUET studies or the darunavir Expanded Access Program (866-889-2074).
- If your CD4 count is very low (under 50, for example), and you feel you cannot risk being on virtual monotherapy by joining the DUET studies, ask your doctor to contact Tibotec at info@tibbe.jnj.com to discuss a Single Patient IND (investigational new drug) for etravirine, along with the darunavir EAP.
- Wait for trials of experimental integrase inhibitors. Merck’s trials of MK518 are open now, and Gilead’s trials of GS 9137 will open soon (check trialssearch.org for details). The Merck trial provides a 33% chance to be on approved drugs only.
- Wait until darunavir gets approved (hopefully in the next few months), and MRK 518 becomes available through an expanded access program, hopefully later this year.

won’t let you access their new drugs through early access programs if you meet the criteria for their clinical trials. Exceptions are sometimes made for people who live too far from a trial site, but this is difficult to do. Activists have pushed for years to allow people with very low CD4 counts to get new drugs without risking being randomized in a clinical trial, but have not had much success.

When someone has highly resistant HIV and a falling CD4 count, the lure of a new drug – especially if it’s in a new class of drugs, such as attachment inhibitors – can be impossible to ignore. But we have to remember that there is a risk/benefit ratio to calculate before deciding to enter a clinical trial. What happens if you get assigned to the placebo arm? What is the potential risk to your health? What if the experimental drug doesn’t work as well as hoped? Where will

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The Hepatitis C Pipeline

by Daniel Raymond

New hepatitis C drugs are desperately needed by people coinfecting with HIV and hepatitis C. About 25 to 30% of people living with HIV in the United States are coinfecting with hepatitis C, with high rates of coinfection among current and former injection drug users. HIV accelerates the liver damage that is caused by hepatitis C, and liver disease from hepatitis C has become a leading cause of death among people with HIV.

Current treatments (48 weeks of pegylated interferon and ribavirin) have considerable side effects and limited success in people living with HIV. People who achieve a sustained virologic response (SVR) – defined as an undetectable viral load six months after the end of treatment – appear to permanently clear the virus, greatly reducing their risk of developing liver cancer and end-stage liver disease. But studies of treatment in coinfecting people have found SVR rates of 27 to 40%, significantly lower than SVR rates in HIV-negative people with hepatitis C. Also, treatment is even less likely to work in coinfecting people with the most common strain of hepatitis C, genotype 1. For this group, SVR rates range from 14 to 29%.

The reasons for poorer treatment outcomes in coinfecting people are not fully known. People living with HIV have higher hepatitis C viral loads than those who are HIV negative, along with varying degrees of immune dysfunction that may hinder the ability of treatment to clear the virus. Coinfecting people also have difficulties tolerating treatment, which can cause a range of side effects that includes depression and irritability, fatigue, anemia, flu-like symptoms, and decreases in infection-fighting white blood cells. As a result, anecdotal reports suggest that relatively few coinfecting patients receive hepatitis C treatment. Barriers to treatment extend beyond the limitations of current therapy – many liver doctors have been reluctant to treat people with histories of addiction, and many HIV doctors lack experience with the demands of managing patients taking hepatitis C medications.

The good news is that many companies are developing new hepatitis C treatments, and several new drugs now in clinical trials may reach the market in the next few years. The drugs furthest along in development include alternative forms of interferon and ribavirin, which may increase treatment efficacy or reduce side effects. The most promising new agents, however, are drugs that directly target the hepatitis C virus, similar to the way antiretroviral drugs target HIV. These compounds, which include protease inhibitors and polymerase inhibitors, have generated significant excitement in the hepatitis C community for their potential to revolutionize treatment.

An ideal hepatitis C drug would dramatically increase the odds of achieving an SVR – particularly for people with genotype 1 (which accounts for 70% of infections in the U.S.), since 70 to 90% of people with genotypes 2 and 3 respond to current therapies. Better drugs would also help coinfecting people, along with African-Americans and people with cirrhosis (advanced liver disease) – groups that also have low success with pegylated interferon/ribavirin therapy.

Despite grounds for optimism, hepatitis C drug development has seen a number of disappointments, with once-promising new drugs abandoned because of unexpected side effects, limited antiviral activity, or poor absorption and metabolism. Two of the more advanced drugs described below – virmidine and valopicitabine – have recently suffered setbacks, and not all of the new agents discussed in this article may ultimately reach the market. Moreover, none of these drugs have been studied so far in people coinfecting with HIV, who are typically excluded from clinical trials of new hepatitis C agents, although some companies have announced plans to begin coinfection studies prior to submitting their drugs to the FDA for approval.

Albuferon

Albuferon (albumin-interferon alpha 2b) is an interferon designed to stay in the

body for longer periods of time than other interferons, allowing for less frequent dosing. In contrast to the pegylation technology used by Roche and Schering, Albuferon fuses interferon to albumin, a protein found in the human body. In theory, this could allow Albuferon (administered, like the other interferons, by injection under the skin) to be dosed once every two weeks, or even once every four weeks. Less frequent dosing may improve treatment efficacy by extending the period during which the drug is active, or increase tolerability – many side effects of interferon are most intense in the first two days after each injection.

Human Genome Sciences recently reported early results of two studies of Albuferon. The first study, involving 458 people with hepatitis C genotype 1 and no prior hepatitis C treatment, compares three different doses of Albuferon to Pegasys, with ribavirin, for 48 weeks. In hepatitis C treatment, a significant drop in viral load after 12 weeks of therapy is referred to as an early virologic response, which predicts the likelihood of achieving an SVR. People who don't become undetectable at week 12 of hepatitis C treatment, or who don't experience at least a 100-fold (2 log) drop in hepatitis C viral load, have very little chance of an SVR after a full course of therapy.

In the first Albuferon study, early virologic responses were seen in 89% of people receiving Pegasys, compared to 84% of those taking 900mg of Albuferon every two weeks, 90% of those taking 1200mg of Albuferon every two weeks, and 76% of those taking 1200mg of Albuferon every four weeks. The company hopes to explore higher doses taken every four weeks to improve response rates. Side effects to date have been generally similar across the four treatment groups, with chills reported more often in those taking Albuferon compared to Pegasys.

The second study compares five different doses of Albuferon (900 mg, 1200 mg, 1500 mg, and 1800 mg, all given every two weeks, or 1200 mg every four weeks)

for 48 weeks in combination with ribavirin, in people who have not responded to prior HCV treatment. Of the 71 people taking one of the three lower doses, 30% had undetectable hepatitis C viral loads at the end of treatment (SVR data have not been reported). Higher doses have not shown a clear advantage, and side effects were generally similar in all dose groups.

Albupheron appears unlikely to replace Pegasys and Peg-Intron unless further research demonstrates a clear advantage in effectiveness or side effects. The convenience of injecting every other week may prove less meaningful to doctors and their patients than the established body of data and clinical experience supporting the pegylated interferons. An interferon that requires only a monthly injection would be more attractive, but if higher doses of Albupheron are needed, they may produce greater side effects. Albupheron could reach the market in 2010. Human Genome Sciences has not announced plans to study Albupheron in HIV-coinfected people.

Viramidine

Viramidine, being developed by Valeant Pharmaceuticals, is a pro-drug of ribavirin, which means it converts to ribavirin in the liver. It was designed to overcome one of ribavirin's major side effects: anemia. Initial research comparing viramidine to ribavirin showed that viramidine results in substantially lower rates of drops in hemoglobin, a protein found in red blood cells used to measure risk of anemia. Viramidine may have particular appeal to people coinfected with HIV, who tend to have higher risks for anemia and more difficulty tolerating ribavirin.

Valeant reported results from one of its two large late-stage studies in March 2006, showing that viramidine caused less anemia than ribavirin when used with Peg-Intron in people who had not taken HCV treatment before, but that SVR rates were significantly lower in people taking viramidine than in those taking ribavirin (38% vs. 52%). Valeant suggested that viramidine may, like ribavirin, require higher doses for people weighing more. At this time, the company still intends to submit viramidine to the FDA for approval in 2007, though whether the

FDA will approve the drug without additional studies demonstrating safety and efficacy with higher, weight-based doses of Viramidine is uncertain. Valeant has announced its intention to begin researching Viramidine in coinfecting people later in 2006; given the VISER data, a coinfection study would likely examine weight-based doses of Viramidine.

Valopicitabine

Valopicitabine (NM-283), being developed by Idenix Pharmaceuticals, is a nucleoside analogue developed to inhibit hepatitis C's polymerase enzyme, respon-

“Drugs that directly target the hepatitis C virus, similar to the way antiretroviral drugs target HIV, have generated excitement for their potential to revolutionize treatment.”

sible for viral replication (roughly equivalent to the role of HIV's reverse transcriptase). Idenix reported early results from a study of valopicitabine with pegylated interferon in people who had not taken HCV treatment before, showing that after eight weeks of treatment, 48-56% of people had undetectable hepatitis C viral loads, depending on which dose of valopicitabine they received. Early virologic response rates in a study of people who had not responded to prior HCV treatment showed that those taking higher doses of valopicitabine with pegylated interferon had greater viral load drops than those taking pegylated interferon and ribavirin. Sustained virologic response data will not be available until early 2007.

Idenix announced in March 2005 that the highest dose of valopicitabine used in the studies (800 mg/day) would be abandoned due to an increased incidence of moderate to severe gastrointestinal side effects. Side effects were severe enough that 16% of treatment-naïve participants and 5% of non-responders taking that dose dropped out of the study. While common, nausea and related side effects were mild and temporary for people taking lower doses.

Idenix will conduct more studies of valopicitabine in combination with both pegylated interferon and ribavirin (pending research on drug interactions between ribavirin and valopicitabine), and the company has announced a study in coinfecting persons to begin later in 2006. The launch of a phase III study has been delayed to late 2006 as a result of the discontinuation of the 800 mg dosing, meaning FDA approval could not happen until 2009 at the earliest. Since previous data demonstrated that the 800 mg dose of valopicitabine was significantly more potent in antiviral activity than lower doses, the ultimate value of this drug at more tolerable doses is unclear.

VX-950

VX-950 is a hepatitis C protease inhibitor developed by Vertex Pharmaceuticals that has shown strong antiviral activity in small studies, both alone and in combination with pegylated interferon. In early 2006, Vertex reported that all 12 participants given VX-950 with pegylated interferon and ribavirin for 28 days achieved undetectable viral loads at the end of treatment. They all had hepatitis C genotype 1, and had not taken any prior hepatitis C therapy. While the study participants did not achieve a sustained virologic response (indicating that longer courses of treatment would be necessary to clear hepatitis C), Vertex predicts that the potency of VX-950 may shorten hepatitis C treatment to as little as three months, compared to the current 12 months that is standard for people with genotype 1.

A three-month study comparing VX-950 and pegylated interferon (with or without ribavirin) to pegylated interferon and ribavirin in people who have not taken HCV

(continued on next page)

The Hepatitis C Pipeline *(continued from previous page)*

treatment before is planned for 2006, and Vertex will likely launch an additional phase II study in non-responders. No significant side effects for VX-950 have emerged in the small, short-term studies reported to date; however, the current formulation of VX-950 requires dosing three times a day, and poor adherence poses the risk of emergence of drug-resistant virus. Vertex has set an aggressive timetable for completing the clinical trials necessary for FDA approval, and plans to submit VX-950 to the FDA in 2008. The company has not announced any timetable for starting a coinfection study.

SCH 503034

SCH 503034 is a hepatitis C protease inhibitor in development by Schering-Plough, makers of Peg-Intron. While Schering's drug has not yet demonstrated the dramatic drops in viral load seen with VX-950, SCH 503034 still has considerable potency, especially in combination with Peg-Intron. Side effects are similar to those seen in people taking a placebo pill, with headaches the most commonly reported. As with VX-950, SCH 503034 is taken three times daily, and monotherapy studies have documented the potential for developing drug-resistant virus. Schering has arguably taken a more conservative and methodical approach to the

clinical development of SCH 503034 than Vertex' VX-950 program, focusing on studies of non-responders, while VX-950 has been researched solely in people who are treatment-naïve.

A phase II study is currently under way to evaluate different doses of SCH 503034 in combination with Peg-Intron (with or without ribavirin) in non-responders, with a comparison arm receiving Peg-Intron and ribavirin. When the study opened in the fall of 2005, Schering made the controversial decision to exclude African-Americans, who usually have lower virologic response rates to interferon-based treatment. Schering has subsequently amended the study to add a higher-dose SCH 503034 arm open to African-Americans. Given these choices, Schering has a responsibility to ensure adequate representation of African-Americans in future SCH 503034 studies. As with VX-950, no coinfection studies have been announced, but they will likely be initiated prior to submitting SCH 503034 for FDA approval (expected some time in 2009).

Watching and Waiting

The new drugs described above represent only a small fraction of what's in the hepatitis C pipeline. Many other agents are in development, including additional pro-

tease and polymerase inhibitors from other companies, along with compounds targeting other parts of the hepatitis C viral replication cycle. People coinfecting with HIV and hepatitis C may have several new treatment options by the end of the decade, though the uncertainties of drug development suggest that those with advanced liver disease should not delay hepatitis C treatment until better drugs are available.

Interferon – with all its side effects – will remain the backbone of hepatitis C treatment for years to come, though ribavirin may be replaced in the near future with safer or more potent drugs. Meanwhile, activists are pressing companies to conduct timely, well-designed studies of their drugs in coinfecting people, as well as other groups in need of better treatments (such as African-Americans, people with cirrhosis, and liver transplant recipients), while carefully evaluating their compounds for potential interactions with HIV medications. If all goes as planned, the future of hepatitis C treatment will mean shorter, safer, more effective therapy for all groups.

Daniel Raymond is the Policy Director at the Harm Reduction Coalition in New York City.

Virtual Monotherapy: Can It Be Avoided? *(continued from page 15)*

you be after 6 months in the trial? What is the risk of developing resistance to the new drug? What is the risk of waiting?

There are no clear answers to these questions. The answers have to come from the clinical trials themselves. The real issue is for people with limited treatment options. As grim as things may look, overall, they're much better than a few years ago. At that time, the goal of salvage therapy was just to keep the patient alive for a few more months. Now, we talk about suppressing the virus, even for highly treatment experienced patients.

Recent studies suggest that going off all protease inhibitors – while staying on nukes – may be a good “holding” pattern. This avoids the accumulation of new protease inhibitor mutations, and appears to do a fairly good job of maintaining CD4 counts. In fact, many physicians leave Efavir (3TC) in a patient's regimen even if HIV has developed resistance to it, because Efavir resistance may actually enhance the activity of other nukes. If you still have two or three effective drugs that you can tolerate, ask your health care provider if you should

switch to them. But if you have only one new treatment available, you have to balance any short-term benefit you might get against the value of preserving future treatment options. Check out web sites dealing with salvage therapy such as: aac.org (click on “Your Health Info” and then “Salvage Treatment”); salvagetherapies.org; hivforum.org/projects/antiviral.htm; and hivandhepatitis.com/recent/salvage/1.html.

Some studies show that the decline in CD4 cells is slower in people with highly resistant virus because the virus may be less “fit” (meaning it is less able to infect CD4 cells). Can you afford to wait until the trials reveal more information about a new drug? Is your doctor willing to jump through the paperwork hoops necessary to enroll you in a compassionate access or expanded access program? Ultimately it's a personal decision – so be sure it's an informed decision. Don't count on clinical trials alone to offer you the best care for your individual situation – be aware of all your options.

Bob Munk is a long-time AIDS activist and the Project Coordinator of aidsinfonet.org.

ACRIA Welcomes New Executive Director

Daniel Tietz, a registered nurse and attorney with over two decades experience in nonprofit management and human services, has joined ACRIA as its Executive Director effective March 15, 2006. He succeeds J Daniel Stricker, who stepped down after eleven years of service.

Tietz most recently served as Deputy Executive Director for Operations at the Coalition for the Homeless. During his four-year tenure, he led an agencywide overhaul of the Coalition's organizational structure, systems, and staffing, and helped guide a \$20 million capital campaign.

He also has a strong background in serving people living with HIV and AIDS. As Deputy Executive Director for Day Treatment and Residential Services at Housing Works, he served as chief administrator for that agency's three licensed adult day healthcare centers and two residential programs in Manhattan and Brooklyn.

Prior to joining Housing Works, he served as Director of Housing Opportunities for Persons With AIDS (HOPWA) at the Postgraduate Center for Mental Health, New York City's contractor for HUD funds aimed at providing housing for people living with HIV/AIDS. In addition, he has advocated on behalf of human rights and social justice issues through independent political activity, including campaign management.

With his broad clinical, management, and legal background, and his demonstrated commitment to the underserved and marginalized populations ACRIA exists to serve, Daniel is uniquely qualified to lead the agency into the next phase of the fight against HIV and AIDS.

HIV Health Literacy Program

ACRIA is pleased to announce that the services formerly delivered by our Treatment Education Department – client and staff workshops, individual counseling, technical assistance, and publications – now fall under the aegis of our newly formed HIV Health Literacy Program.

Health literacy is the ability to read, understand, and use basic medical knowledge and information effectively. Functional health literacy is associated with illness-related knowledge, an understanding of disease processes, and treatment perceptions. HIV-positive people with low health literacy tend to experience more frequent and more severe bouts of illness, require more frequent and longer hospital stays, and are less likely to comply with prescribed treatment and care regimens than those whose health literacy is high.

The new name recognizes the breadth of our services and does not indicate any change in our commitment to providing comprehensive HIV healthcare and treatment education to those who need it most.

Community Mapping Initiative

ACRIA's HIV Health Literacy Program, working closely with our Research Department, has embarked on the Community Mapping Initiative, a program to "map" HIV-positive people throughout New York City with regard to a variety of factors affecting their access to care, their ability to participate actively in their own care and make informed decisions, and the concrete effects on their care of the availability of community-based treatment education.

The overall purpose of the program is to form a statistical picture of the health literacy needs of HIV-positive people throughout New York City, to see how those needs may differ in different

groups, and to advocate for those needs. Our aim is to assure that ACRIA's HIV health literacy services are responsive to the needs of those we serve; to examine differences in the needs of different groups, e.g., HIV-positive women of color versus white men, or older versus younger women of color; to develop an advocacy strategy and tools that communicate those needs to policy makers and the general public; and to build public and private support of community-based treatment education services, particularly in communities of color.

People with HIV-positive form not only the target population of the program but its backbone as well, acting as community monitors to collect information and enter it into our computer database for analysis. A detailed questionnaire has been prepared and is being administered at our HIV health literacy workshops at community-based organizations across the city and elsewhere in communities of color. A detailed report, with maps presenting the information graphically, will be prepared and distributed in late June.

The Community Mapping Initiative is funded by a grant from the New York City Communities of Color HIV/AIDS Coalition (NYCCOCHAC).

Medical Centers Invite ACRIA Researchers

The initial findings of ACRIA's groundbreaking study on HIV-positive New Yorkers over the age of 50 – Research on Older Adults with HIV, or ROAH – have been presented at several locations around the city. Dr. Stephen Karpiak, ACRIA's Associate Director for Research, has presented at St. Luke's/Roosevelt, Bellevue, and NYU Medical Center, and is scheduled to talk at Cornell-Weill Medical Center in May. Research Associate Andrew Shippy presented on the Spanish population data from ROAH at the Latino AIDS Forum in Albany in March.

generous contributions

The following persons, corporations and organizations made major donations between January 11 and March 30, 2006 to support ACRIA's research and education efforts:

Anonymous	Donna Karan
Banana Republic	Charles Klein
Boehringer Ingelheim Pharmaceuticals	Albert Messina
Bristol-Myers Squibb Company	Pfizer, Inc.
Randall Drain	Cynthia & Ron Rose
Kay Goldberg	Paul Rykoff Coleman Foundation
In Style Magazine	J Daniel Stricker

Thoughtful donations were made in memory of the following individuals:

Stephen Montgomery
Anne Reynolds
Thomas Saporita

Contributions in support of ACRIA's vital research initiatives were made in honor of the following individuals:

J Daniel Stricker

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