



The Cure: Why, whether, how and when?

by Martin Delaney, Founder

More than three years ago, Project Inform kicked off a campaign to refocus the attention of the patient, activist and research communities on the need for a true cure for HIV disease. The success of combination therapy and treatment simplification seemed to have created a wave of complacency and a sense that, except for side effects, HIV treatment was finally “good enough.” Project Inform has challenged this view ever since. Though the effort was sometimes ridiculed as naïve, a number of influential groups and researchers have now joined the campaign.

Today more people than ever agree that the current standard of lifetime maintenance therapy is not an adequate solution to the HIV epidemic. Several factors made this conclusion more obvious than ever. This article examines four issues about the notion of curing HIV disease: (1) why the goal of curing HIV disease has become so critically important; (2) whether a cure is feasible given current and near future technology; (3) what “cure” means and how it might be achieved; and, (4) when this might be possible. The article also closes with new information about efforts now underway toward reaching this goal.

1. Why is a cure so important?

This may seem obvious to just about anyone with HIV disease, but it has not always been so. Today’s regimens offer dramatically better outcomes than what people typically faced earlier in the epidemic. It might be easy for some to think that the problem of HIV has largely been solved. Not quite. Not even close.

Thankfully, the days of a short-term death sentence are well behind us. With good care and treatment, it’s fair for people with HIV to expect to live out a relatively normal lifespan. Missing from the greatly improved picture are the ways in which HIV disease still complicates the lives of those affected as well as its costs to both the individual and the public.

Today, HIV treatment means a lifetime of using multiple, expensive medications whose long-term side effects can’t be known until they have actually been used long-term. Today’s drugs are easier to use and appear far less toxic, but only a few have been used for 10 or more years. We have yet to learn what the consequences will be of 20 or 50 years of use.

Another thing typically overlooked is the lifetime cost of treatment which currently averages between \$12,000–\$25,000 a year for relatively healthy people with HIV, and much more for those in advanced stages of disease. While these costs have been met in the short-term, we’re only beginning to look at the lifetime costs of being on regimens for up to 50 years. It’s simple: do the math!

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And what about the developing world, where roughly 90% of the world's cases of HIV occur? Despite massive infusions of money, and despite reducing the costs of drugs to virtually that of their raw materials, efforts still only reach a modest percentage of the people worldwide who need treatment.

The US committed more than \$15 billion to HIV treatment in developing countries over the last five years through the PEPFAR program. The World Health Organization, Global AIDS Fund, Clinton Foundation and many smaller groups along with support programs from the pharmaceutical industry have made enormous additional contributions. The reach is still too small and the amount of money needed must be increased many times over to reach even the most vulnerable parts of the infected population.

It has long been hoped that this would only be temporary; that we would have a vaccine and the numbers of people infected each year would finally begin to drop. Sad to say, but the search for a vaccine hit a wall in the last year. In many ways, we may now be no closer to a vaccine than we were 20 years ago. Some of the most prominent scientists in the world are warning us that a vaccine may never be possible due to HIV's unique properties.

At the very least, if there is to be an HIV vaccine, we currently have no idea how to make one. Similarly, great hope was invested in using microbicides — gel-like compounds applied to the areas of sexual contact that hopefully block HIV infection. But so far these have proven about as effective as vaccines, which is to say “not at all.”

Thus, when we take a sober look at the fight against HIV in the developing world, the prospects of lifetime therapy don't look so good either. First, the expenditures by wealthier nations will have to drastically increase, and then these sums must be sustained for the next 50–100 years, assuming there's no vaccine in the near future. We must ask: how likely will developed nations continue this level of support for as long as it's needed?

Sadly, the answer is not very likely. For one, there's little precedent for sustained medical effort in developing nations, let alone one as expensive, difficult and lasting as fighting HIV is. Secondly, the costs are so large they may not be sustainable at all. Even the great private funds like that of Warren Buffet will be bankrupted over time by this fight.

In short, lifetime therapy is not a realistic solution for HIV disease even in the US and Europe let alone the developing world. The situation can only worsen if unexpected long-term side effects appear over time.

It should be abundantly clear: the only way to effectively conquer the epidemic is to cure the disease. We cannot coddle the virus with a lifetime of drugs. People with HIV should be enormously grateful to all those who have contributed to developing the drugs we have today. Millions more would have died without them. But their utility is limited and they're not a true long-term solution. The goal of fighting HIV for the first 25 years was to create and distribute effective anti-HIV drugs. The goal of the coming years must be to get people OFF the drugs and back to a state of normal health.

2. Is a cure feasible?

It is one thing to conclude that a cure is needed, and perhaps it's the best and only real solution to the epidemic. It is quite another to say that it's possible to create one.

Many scientists argue a cure is unrealistic with any conceivable technology. They quickly insist that a cure requires the complete eradication of HIV. Every copy of it must be prevented from infecting a cell, and every cell that already contains HIV must die off or be destroyed. Otherwise, they believe, the infection will just start up all over again.

In memory of...

We dedicate this issue of *PI Perspective* to the following individuals. Their memories lives on in the work that lies ahead.

Scott Strang, RN
Ray Wilie

While this sounds reasonable at first, is it necessarily so? It is important to ask scientists, “Just what data support this? What study or observation concludes that you have to eliminate every last copy of HIV or infected cell to reach a point where it’s no longer a problem?” There are no such data, no such studies. It is a belief, not a scientific fact.

The hints we have from data largely suggest that the opposite may be true. Many viruses peacefully co-exist in the human body, though in some cases they can be highly destructive. Two good examples are CMV and JCV. CMV can cause blindness and death; JCV can cause a horrible form of dementia that leads to death. Yet each is quietly present at low levels in most people and does little or no harm except in rare circumstances.

What about HIV? In primates, the equivalent of HIV is called SIV, and it often replicates freely yet does not cause harm or become AIDS. It’s how the immune system reacts to it that causes the harm. Moreover, we know there are literally thousands of humans with HIV who, due to a combination of factors, either maintain only low levels of HIV or simply don’t get sick from it. They may be a small minority, but they prove the point: HIV, even in the absence of treatment, is not always destructive.

The data simply do not support the notion that the only way to survive HIV is either through lifetime therapy or by complete eradication of virus. It would be ideal to rid the body of HIV, but an effective cure may NOT require this. If anything, the data suggests the opposite.

We see people repeatedly exposed to HIV who never become productively infected. We see that reducing, though not eliminating, virus in a pregnant woman almost completely eliminates the risk of her passing the infection onto her child. We know that true long-term non-progressors, or *elite controllers*, sustain some level of HIV infection but show little evidence of clinical illness.

Perhaps a harmful case of HIV requires a certain level of virus before it becomes destructive. Maybe treatment can push the level of virus low enough that it no longer matters. Possibly some of the new properties shown by drugs like CCR5 antagonists and integrase inhibitors may change the underlying conditions that make harmful HIV replication happen.

Dr. Steven Deeks, a key researcher from the University of California, summed it well at a recent Project Inform Update Town Meeting when he said, “Beware of grey haired scientists who tell you something is impossible.” He is hardly alone.

There’s a growing cadre of young investigators at universities, the NIH and drug companies who believe a cure is indeed feasible, and perhaps sooner than many think. It is instructive to remember that shortly after HIV was found to be the cause of AIDS, some researchers claimed, “It will be impossible to treat this disease at all.” Within 21 months, the first drug was approved by the FDA. Little more than 20 years later, scientists claim that people with HIV and access to treatment could expect to live a normal life span. A cure is not only possible; it is the next step in HIV research.

3. How can HIV be cured?

It is admittedly premature to pronounce that one approach or another is the most likely avenue to curing HIV. Instead, there are a number of possibilities. What we need are some serious programs to develop and test them. So far, the most widely tested approach has used just antivirals, alone or together with another kind of drug to try to eradicate HIV.

Scientists back in 1996 thought it would be enough to simply give people the strongest antivirals for several years in a row and this would gradually eliminate even the last copies of HIV. They were wrong, but this led to the discovery that HIV was being sustained, in relatively small amounts, in

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“reservoirs.” These were generally inactive cells, like memory T-cells, which the immune system only rarely activates and uses. They’re largely unaffected by HIV drugs and the immune system. For some reason they can only be reached when they are activated.

This led to a second approach, one that was predicted in the 1980s. It also used the most potent antivirals and added a second type of drug to activate these reservoir cells. This ultimately proved dangerous, as it activated all the cells in the body. Still, some scientists believe we haven’t given this approach a fair trial. They argue that perhaps we need to use this approach more slowly, but repeatedly, in hopes of reaching all the cells in the reservoirs, but not all at once.

Although neither approach succeeded, they showed that when patients were treated in this way, they would sometimes remain free of active replication for a month or longer without therapy. A similar early attempt used the immune modulator IL-2, which is T cell stimulator, to achieve this goal. This too seemed to delay the return of viral replication in people whose antiviral treatment was interrupted, but it eventually failed.

Thus, attempts at eradication have neither succeeded, nor completely failed. Several studies are now underway to further test eradication theories by using the new integrase inhibitor drugs. Their different mechanism of action offers some theoretical benefits compared to previous antivirals. Remember, though, that we really don’t know whether a “cure” actually requires complete eradication.

A recently reported case study from Germany described what happened when a patient was given a stem cell transplant, for treating cancer, by using cells from a donor who lacked the genes that cause the body to make the CCR5 receptor favored by HIV. This case study is described in more detail on pages 8–9 of this issue.

More than 300 days after the transplant and any use of antivirals, the patient still shows no evidence of HIV replication, either by standard viral load testing or a more sensitive test that measures what’s called pro-viral DNA. Though the investigators are not calling it a cure, they continue to follow the patient to see whether or when HIV replication might restart.

At the very least, it seems to prove the concept that when viral levels are greatly reduced, even if not eliminated completely, the body seems to keep HIV well in check for long periods without antivirals. It would be difficult to find enough donors who have this very special type of genetic mutation, so this exact procedure is not practical for large numbers of people. A similar goal could be achieved through gene therapy, something which eventually could be applied to large numbers. Other types of gene therapy also offer hope in the pursuit of a cure.

Yet another approach seems to offer hope, even if it proves necessary to go after every cell that has been infected by HIV. A German group revealed a new technology, on a laboratory level, which is able to extract viral genetic sequences that have been integrated into human cells. It’s a long way from being a practical therapy, but again, it shows proof of the concept.

Other scientists are working on ways to suppress the inflammatory processes triggered by HIV infection. Some believe that it is inflammation rather than any unique activity of HIV that makes it harmful. They believe it causes harm primarily because it causes cells to release inflammatory proteins, which in turn harm the body. If this is correct, turning down or turning off the inflammation may be enough to change HIV into a harmless virus.

These and other approaches all rely on a simple definition of what curing HIV must mean. Cure, in this way of thinking, may not mean absolute elimination of the virus. Rather, it simply requires reaching a state where either there’s no measurable HIV replication despite withdrawing therapy, or where the immune response to HIV is changed in ways that no longer harm the body or immune system.

A cure also cannot be expected to automatically repair any damage done to the immune system when HIV was active. It would be great if that could be achieved, but it's not a standard we demand of other cures. Sometimes a cured disease leaves damaged tissue or cells behind. Sometimes the body fixes them over time; sometimes it doesn't. Antiviral drugs aren't completely fixing the immune system now, so we cannot demand that a cure will do it either.

4. When can a cure happen?

This question is impossible to answer. At best, prediction is a tricky business. However, a number of the more enthusiastic researchers seeking a cure believe that the solution may be closer than most believe. Claims that it won't be possible until far in to the future are based on the false definition of cure, the one that demands absolute eradication. Once we realize that this is not required, the cure doesn't seem so very far away.

It's now routine to reach HIV levels below 50 copies. Studies with new drugs are now using a test that measures down to 5 or 10 copies, and there's evidence that the drugs are succeeding at this level. Researchers will need to retest various eradication approaches using these new therapies. We really don't know what happens when HIV is suppressed this low for long periods.

Similarly, a few first generation gene therapy studies are well underway and near completion. These may not be the total solution but could well point us there, as does the German stem cell transplant program. The most optimistic researchers we have spoken to believe we will see the first evidence of a cure in as soon as 5 to 10 years.

A few argue that it has already happened, but our ability to see and measure it lags behind. It is even possible the immune system itself has done the job in some cases, but we just don't know it. Why? Because once a person gets truly well, they are seldom studied. We simply would not know if there have been people all along for whom the natural immune response has been sufficient.

We believe this process can and must be accelerated. It currently receives very little funding — just a tiny fraction of the amount spent developing new antivirals. We are aware of only two pharmaceutical companies that are actively pursuing cure-based research. Merck has a lab dedicated to studying eradication in the same systematic way they develop a new drug. Tibotec/J&J is already engaged in a very interesting gene therapy study that may help point the way. We'd like to see every drug company invest in this area, if for no other reason than the fact that it might offer the last hope for big profits in the fight against AIDS.

There are now 24 antivirals on the market. Each gets only a modest portion of the revenue generated by only about 10% of people with HIV. If the lure of profits is what it takes to generate interest in the cure, so be it. While a cure would certainly end the drug companies' revenue stream from lifetime therapy, several have argued that there are far more profitable areas of medicine and drug development than HIV. They would make more money working in those areas once their patents in HIV expire.

Given the failure of vaccines and the difficulties faced in microbicide development, along with the prohibitive costs of lifetime therapy, we believe research funding must be redirected toward the kind that can result in a cure. This will require a large change in how research is funded, and it requires new insights from basic science as well as clinical research.

Efforts are underway to make this happen. In December 2008, more than 125 scientists from around the world came together in a meeting dedicated to unraveling the challenge of HIV persistence and eradication. These scientists, along with a few activists and foundation representatives, are committed to this type of research.

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amfAR has already issued a series of program grants for work in this area. A collaboration of community groups is also organizing a scientific meeting that will take place in the fall to develop plans and strategies to enhance and support this research. TAG (Treatment Action Group), amfAR, FAIR, The Forum for Collaborative HIV Research, and Project Inform have banded together to organize and help fund this meeting, which may be the first of several. amfAR is considering a second round of grants to support such work, and FAIR (the Linda Grinberg Foundation for AIDS and Immune Research) will fund another group of proposals. Collectively, we hope to further influence the Division of AIDS at the National Institute of Allergy and Infectious Diseases to increase its commitment to this type of research.

As we shift our thinking in pursuit of a cure, we will not abandon interim needs. There is still a need for better and less toxic antivirals. There's a profound need to figure out how to make the best use of the new drugs we've recently gained. Project Inform is pursuing these needs on a separate but parallel track through another scientific conference we're organizing for the fall, called HAART 2.0. This meeting will help develop strategies for testing new paradigms of treatment with current drugs. These include such things as one- and two-drug regimens, eliminating the most toxic agents, and reducing the use of drugs that harm the liver or heart. Some of what we learn through that process will not only benefit patients in the short-term but will also contribute toward the final push for the cure.

A personal comment

As many of you know, I officially retired from my program role at Project Inform in January, but I have not left AIDS work. I am committed to making this focus on a cure the core of my work in the final chapters of my life. Like others at Project Inform and many other organizations, I believe that we can and must find a real cure. There's no other real solution on the horizon. This is as true for the US and Europe as it is for the developing world. We won't have a cure unless we believe in it and pursue it as our primary goal. We're going to have a cure, and it will happen in our lifetimes.

Project Inform considers its role in a national strategy to eliminate the epidemic

by Dana Van Gorder, Executive Director

In February 2008, Pfizer invited a substantial group of Executive Directors of the nation's HIV/AIDS agencies to gather at their Research & Development headquarters in Groton, Connecticut. The meeting had two principal goals: for us to hear from Pfizer about the hope and challenges that characterize the search for increasingly effective treatments for HIV infection; and to consider how the United States will continue to finance the cost of HIV care and treatment.

I was given the great opportunity to lead a panel of HIV healthcare finance experts in a look at current and future funding issues for the Ryan White Program, Medicaid and Medicare. The panel also provided me with the opportunity to share in a conversation taking place at Project Inform about how, in years to come, the nation will move beyond managing the ongoing epidemic to truly controlling and ending it.

Today, there are some 1.2 million HIV-positive Americans. In the coming months, the CDC is expected to revise its estimate of the number of people who become newly infected each year from

its current rate of 40,000 to perhaps 60,000 or more. In so doing, estimates of the total number of HIV-positive Americans may also increase significantly.

Some 17,000 Americans die each year as a result of HIV. And so, if we maintain our current response to the epidemic, there will be at least 1.63 million HIV-positive people in the nation in 2018.

Nearly two-thirds of HIV-positive people will need to turn to publicly funded programs to pay for care, treatment and social services. Today, the cost to the federal government alone of care and social support for HIV-positive people is \$13 billion. Project Inform's Public Policy Department works tirelessly and effectively to advocate for the protection and expansion of all public programs that provide care and treatment to the most vulnerable people living with HIV. And yet we know all too well that current spending is inadequate to assure comprehensive, quality care for even the existing patient load. Among those currently in care and treatment for HIV, many are receiving inadequate services as a function of who they are and where they live.

The CDC estimates that fully 25 percent of HIV-positive Americans do not know their HIV status because they have never been tested or have not been tested recently enough. And an estimated 20 percent of people who do know that they are HIV-positive are not currently receiving care or treatment.

If, then, we had a meaningful national strategy to help the 45 percent of HIV-positive people to enter care who are not currently receiving it; if we were to provide all existing HIV-positive people with quality care and support services; and if we add 430,000 people to the rolls of those who will need HIV-related treatment and social services, what would be the true public cost of the care and treatment of HIV in the United States in 2018? Logic suggests that the answer is at least a staggering \$19.5–\$26 billion a year.

At this cost, does the political will exist to take the measures necessary to truly control the HIV epidemic? Can we ignite a second movement in this country to create that political will? If we truly want to rid the nation of this scourge, we will have to.

A key topic of conversation at the Pfizer meeting was the current plan to develop a National AIDS Strategy. Project Inform wholeheartedly supports the goal of creating the Strategy, and we are honored to be a part of the first organizing meeting for the effort taking place in New York this coming April. For us, an effective Strategy will go beyond addressing the many needs and goals that would enhance current efforts to address HIV/AIDS. The Strategy should truly be strategic, comprising a focused and detailed public health plan that describes how we will control and then eradicate HIV domestically. The Strategy should answer the following questions:

- Exactly how will we assure that all HIV-positive Americans currently unaware of their HIV status are tested for HIV, and that all Americans are routinely tested for HIV in the future?
- How will we ensure the entry of all HIV-positive people into quality, affordable healthcare who choose to be in care and treatment, and how will we eliminate disparities in healthcare and clinical outcomes for women, people of color and low-income people with HIV?
- How, through national healthcare reform, by enacting the Institute of Medicine's recommendation that the Ryan White Program become an entitlement program, or by some other means, will we guarantee access to comprehensive, quality care and treatment for all HIV-positive Americans?
- How will we eliminate barriers to the research and development of additional therapeutics for HIV disease, with an emphasis on those that go beyond controlling HIV replication to an actual cure for HIV infection?

- How will we reduce by at least three-quarters the number of Americans who become infected with HIV annually through enhanced behavioral prevention and a major effort to prevent HIV using biomedical approaches? What will be the cost of this effort, and how will it be financed?

One thing is painfully clear about the challenge that HIV/AIDS advocates face in assuring adequate future funding for the care, treatment and support services needed by HIV-positive people. If we do not dramatically slow the rate at which additional people are becoming infected with HIV each year, we cannot possibly hope to finance the total cost of addressing HIV in the United States.

Project Inform has not historically been involved in HIV prevention related activities, except that our support of HIV-positive people entering care and treatment clearly helps to reduce overall community viral load and with it the likelihood of HIV transmission. But today, we are discussing ways in which to add to our existing portfolio of vital advocacy activities meaningful support for biomedical approaches to HIV prevention — that set of strategies that will bring HIV treatment and prevention together to further reduce the incidence of HIV.

Among the possibilities Project Inform is considering for advocacy of biomedical prevention are the following. To actively support efforts to:

- increase testing among individuals at high-risk for HIV infection and encourage them to enter treatment in order to preserve their health and avoid transmitting HIV to others;
- encourage all HIV-positive people to consider early treatment for HIV with these same benefits;
- determine the possible effectiveness of Pre-Exposure Prophylaxis (PrEP) in preventing HIV transmission and an expansion of Post-Exposure Prophylaxis (PEP) in preventing HIV infection, as well as advocate for the public financing of these prevention strategies;
- develop and deliver effective and affordable microbicides, both vaginal and rectal;
- encourage the widespread detection and treatment of sexually transmitted infections, including herpes in HIV-positive individuals; and
- although it is not precisely a biomedical prevention activity, assure the expanded availability of syringe exchange programs throughout the United States.

I look forward to keeping the readers of *PI Perspective* well informed both as Project Inform makes decisions about its leadership of biomedical HIV prevention and as the effort to develop a National AIDS Strategy proceeds. And I welcome your thoughts about how this agency, and the nation as a whole, can create a more muscular movement to advance our nation from managing the HIV epidemic to eradicating it. Please be in touch with me at dvangorder@projectinform.org.

Update from CROI 2008 — Stem cells: Progress towards “the cure”?

by Martin Delaney, Founder

For the last three years, Project Inform has spearheaded a renewed call for research that seeks to find a real cure for HIV disease, rather than settling for lifetime maintenance therapy on drugs. A case study from the Medical University of Berlin reported at CROI 2008 offered intriguing results from a stem cell transplant, an approach that was tried before but without success.

Previous stem cell transplant programs primarily sought to replenish the immune system with new cells. After the transplant, these programs typically counted on using anti-HIV therapy to protect the new immune cells.

However in this case, a person who had been living with HIV since 1995 underwent treatment with stem cells for a relapse of *acute myeloid leukemia*, a cancerous growth of a type of white blood cell. Since the patient was HIV-positive, researchers sought out a stem cell donor whose cells lacked the CCR5 receptor that HIV commonly uses to get into immune cells.

Research shows that people who lack this receptor are highly resistant to HIV infection. We inherit two copies of the gene that makes this receptor, one from each of our parents. If a copy from one parent is defective, a person generally becomes a slow progressor if infected by HIV because of the lower number of functional CCR5 receptors. If copies from both parents are defective, a person is highly resistant to HIV infection or, if infected, typically becomes a long-term non-progressor.

Only a small percentage of people, usually of European descent, have this fortunate genetic trait. The importance of the CCR5 receptor is well shown in studies of the drug Selzentry (maraviroc), which blocks the receptor and slows HIV reproduction. This patient's own cells had the usual amount of the CCR5 receptor, and the strain of HIV in his blood was the type that used the receptor. The German researchers hoped that by using stem cells that lacked the ability to make the receptor, the newly restored immune cells might better resist HIV infection and replication.

Researchers stopped the patient's HIV regimen at the day of the stem cell transplant and have not restarted it. Ongoing studies 145 days after the transplant showed that the patient's mucosal CD4+ cells now lack the CCR5 receptor. More importantly, starting 61 days after the transplant, the patient's HIV level fell below the limit of detection and has remained undetectable since then. Similarly, they can no longer find evidence of pro-viral DNA in peripheral blood, bone marrow or rectal mucosa.

Pro-viral DNA is HIV genetic information that has been incorporated into a cell's own DNA, and is capable of producing new virus. These tests remain negative out to nearly 300 days (285 days as of CROI), despite the absence of any HIV drug treatment since the stem cell transplant. Before the transplant, the patient required a normal 3-drug regimen.

The researchers are making only the most modest statements about what this means, saying, "this finding provides a possible therapeutic option for HIV-infected patients." Several physicians and researchers we spoke with were much more enthusiastic. At the very least, this strongly reinforces the importance of blocking, or eliminating, the CCR5 receptor.

Few potential donors could offer stem cells that not only match the patient's but also lack the CCR5 receptor, though there may be ways to clone such cells. Gene therapy could perhaps be used to alter stem cells. For now, follow-up of this case is important to see when, if ever, there is a return of HIV replication. The German researcher we spoke with said that it would perhaps be possible to find HIV in the patient using other methods, but as long as there was no evidence of ongoing replication on HIV RNA tests, they would not restart HIV therapy.

This is another one of the kind of "one step at a time" approaches that we hope will one day lead to an outright cure of HIV infection, a state in which people who were once actively infected can remain "HIV undetectable" without any ongoing use of therapy. We urge other researchers to replicate or build upon this impressive case study, and we salute the patient and his doctors for taking this bold approach to treating HIV disease.



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Update to the Federal Guidelines for treating HIV disease in adults and adolescents

by Paul Dalton, Director of Treatment Information & Advocacy

In early 2007, the DHHS Guidelines panel met and agreed to a complete review and update of the guidelines. Members of the panel, which include treating physicians, researchers, government officials and community members, were assigned to various subcommittees to review the document and recommend changes to the full panel. Two sets of updates have been issued: one in December 2007 and one in January 2008. This article reviews the changes thus far.

When to start

The panel made subtle, but important changes in the recommendation for when to start HIV treatment. The previous guidelines recommended that treatment be discussed when a person's CD4 count fell below 350 cells/ml, and be started in anyone whose count fell below 200. The guidelines now recommend starting treatment before a person's CD4 count falls below 350. Treatment is also recommended — regardless of CD4 count — for pregnant women, anyone with an AIDS-defining illness, people co-infected with hepatitis B virus (HBV) that requires treatment, and anyone diagnosed with HIV-associated nephropathy (HIVAN).

Many scientists, doctors and activists now think that HIV treatment should be started earlier than the current recommendations. Citing a lack of conclusive data, the panel was not willing to make this recommendation. Rather they included a discussion about the possible benefits and risks of starting treatment at higher CD4 counts.

The major points of the discussion were:

- The risk of death or serious illness in people with CD4 counts above 350 is low, so any benefit on these outcomes from starting treatment at high CD4 counts is likely to be small.
- There are data — for example the ATHENA cohort — which show that people who start HIV treatment with CD4 counts above 350 are more likely to achieve and maintain CD4 counts above 800.

drug i.d. chart

TRADE NAME	GENERIC NAME
Protease inhibitor	
Agenerase	amprenavir
Aptivus	tipranavir
Crixivan	indinavir
Invirase	saquinavir
Kaletra	lopinavir + ritonavir
Lexiva	fosamprenavir
Norvir	ritonavir
Prezista	darunavir
Reyataz	atazanavir
Viracept	nelfinavir
NRTI (nucleoside) and NtRTI (nucleotide) analog reverse transcriptase inhibitor	
Combivir	lamivudine + zidovudine
Emtriva	emtricitabine (FTC)
Epivir	lamivudine (3TC)
Epzicom	lamivudine + abacavir
Retrovir	zidovudine (AZT)
Trizivir	lamivudine + zidovudine + abacavir
Truvada	emtricitabine + tenofovir
Videx	didanosine (ddl)
Videx EC	ddl enteric-coated (ddl EC)
Viread	tenofovir
Zerit	stavudine (d4T)
Ziagen	abacavir
NNRTI (non-nucleoside) reverse transcriptase inhibitor	
Intelence	etravirine
Rescriptor	delavirdine
Sustiva	efavirenz
Viramune	nevirapine
NRTI + NNRTI combination	
Atripla	efavirenz + emtricitabine + tenofovir
Entry inhibitor	
Fuzeon	enfuvirtide (T20)
Selzentry	maraviroc
Integrase inhibitor	
Isentress	raltegravir

- Similarly, in the Johns Hopkins Cohort, people who started treatment with CD4s below 350 were less likely to achieve and maintain CD4 counts above 500.
- Early HIV treatment has been shown to reduce HIV transmission rates.

Factors weighing against early treatment would be:

- the necessity of life-long treatment,
- the lack of long-term data on most HIV drugs,
- the potential for developing drug resistance,
- the interference with quality of life, and
- the potential for long-term side effects.

The best time to start HIV treatment remains one of the major unanswered questions in HIV treatment. There are two significant obstacles to answering this question: one philosophical and one practical. Philosophically, there's no consensus that there even could be a single recommendation that will be appropriate for all, or even most, people with HIV. Some say that important factors needed to guide treatment decisions vary significantly from person to person. No recommendation, or set of recommendations, could possibly account for this. Others would counter that, while a person's unique situation must factor into all treatment decisions, broad recommendations can nonetheless help guide and inform anyone making the decision to start HIV treatment for the first time.

Philosophical considerations aside, there's a practical issue with the data. The guidelines panel's recommendations are data driven. The gold standard of bio-medical research is the prospective, randomized, controlled clinical study. No such study exists on the question of when to start. Designing and implementing one is challenging. Such studies would need to be large and long-term to gain useful information. This begs the question of the applicability of the information once the study is done. For example, if a 'when to start' study had been done in the late 1990s, final data would just now be reportable. We would have a lot of information on Crixivan (indinavir), Viracept (nelfinavir) and Zerit (stavudine) regimens. How helpful would that be given the range of classes and individual drugs that are now available?

The panel's recommendation to start treatment when CD4 counts fall to 350 was based on data that show a clear benefit to people starting treatment at this level. The document cites two studies in particular. The first is the ART cohort — a large, multi-centered study with over 60,000 person years of follow-up. (A *person year* is a statistical measure that simply multiplies the number of people in the study by how many years each person has been followed.) The ART study found that people who started treatment with CD4 counts between 200 and 350 had a much higher risk of opportunistic disease and death than those who started with CD4 counts below 200.

They also cited the SMART study — a large, prospective, randomized, controlled trial of continuous HIV treatment vs. CD4 guided intermittent treatment. SMART was halted early when it was found that people in the intermittent treatment group had higher rates of opportunistic and non-opportunistic diseases and death.

The data were similarly strong for pregnant women, people with HIVAN, and HBV co-infection that required treatment. The use of HIV treatment by pregnant women has reduced the risk of mother-to-child HIV transmission from around 25% to less than 1% in some settings. The risk of kidney damage in people with HIVAN has been shown to be more closely related to being off treatment than either HIV levels or CD4 count.

The situation for people with HBV co-infection requiring treatment is a bit different. Many of the most common drugs used to treat HBV have anti-HIV activity as well. If a person were on HBV drugs, like Viread (tenofovir), Epivir (lamivudine) or entecavir, they run the risk of developing resistance to HIV drugs.

Project Inform believes that HIV treatment decisions should be driven by a combination of the best available data a person's unique life circumstances and medical history, and personal preference. We also recognize that in most diseases, particularly infectious diseases like HIV, earlier treatment usually leads to better treatment outcomes. There is no evidence to suggest this would not be true for HIV disease.

The main factors leading to delaying treatment in HIV disease have been the demands of life-long treatment, concerns over side effects, and the fear of drug resistance. With over two dozen HIV drugs on the market today — many of which are simpler to take and seem to have fewer side effects than the older generation of drugs — this situation may be changing.

In addition to protecting the health and well-being of the person living with HIV, ARV treatment also reduces the risk of HIV transmission. While treatment decisions should be primarily guided by the needs of a person living with HIV, the health and well-being of the larger community can also benefit. This could be particularly important for people in relationships with an HIV-uninfected partner, or people with multiple sexual partners.

What to start

The recommended first line treatment paradigm remains the same: a backbone of two NRTIs plus either a boosted PI or an NNRTI. The list of drugs appropriate for first line use was changed significantly. The fixed-dose combination pill Combivir was downgraded from *preferred* to *alternative* based largely on lipoatrophy data. Epzicom was upgraded from *alternative* to *preferred* based largely on the availability of HLA testing that reduces the fear of abacavir hypersensitivity reactions. Several protease inhibitors changed position as well.

Below is a summary table. Note that this is only for first line use.

CLASS	PREFERRED	ALTERNATIVE	NOT RECOMMENDED
NRTIs	Truvada Epzicom	Combivir ddl + 3TC or FTC	d4T
NNRTIs	Sustiva	Viramune	Rescriptor Intelence
Protease Inhibitors	Reyataz—boosted Lexiva—boosted (2x/day) Kaletra (2x/day)	Reyataz—unboosted Lexiva—unboosted Lexiva—boosted (1x/day) Kaletra (1x/day) Invirase—boosted	Invirase—unboosted Viracept Aptivus Prezista

The decision to move Combivir from *preferred* to *alternative* was based largely on data that showed a higher risk of *lipoatrophy*, or loss of fat (usually in the face, arms, legs and buttocks) in people taking regimens that contain zidovudine (AZT), which is one of the drugs in Combivir. Of all the NRTIs in wide use, zidovudine carries the highest risk of lipoatrophy. The combination of Videx EC (didanosine, ddI) + Epivir is also listed as an *alternative*.

The decision to move Epzicom from *alternative* to *preferred* was due to the development of a genetic test, called HLA testing. This can fairly accurately predict a person's risk of developing a serious allergic reaction to abacavir, which is one of the drugs in Epzicom. This reaction, called *abacavir hypersensitivity reaction* or HSR, has been a major deterrent for many people to use this drug. Recently several studies, including PREDICT and SHAPE, have shown that a genetic variation, called HLA-B*5701, is powerfully predictive of a person's likelihood of developing abacavir HSR. The updated guidelines include guidance on using HLA testing; emphasizing it should not be used as a substitute for clinical vigilance.

A recent finding reported elsewhere in this issue has reopened the question of Epzicom's position in the guidelines. As reported on page 17, the large cohort D:A:D study found an increased risk of heart attack (*myocardial infarction*) for people taking abacavir and another NRTI, Videx. The overall risk was still small, but the difference was considered statistically significant. This finding was surprising. Some have questioned the significance, pointing out that other studies looking at abacavir haven't found an increased risk of heart attack. Whether this new finding leads the guidelines panel to change their recommendations on using abacavir remains to be seen.

The Norvir (ritonavir) boosted protease inhibitors Lexiva (fosamprenavir) and Reyataz (atazanavir) now join Kaletra as preferred options for first line protease inhibitors (PIs). Boosted Invirase (saquinavir) was moved from the *not-recommended* to *alternative* category. These changes resulted from a series of head-to-head studies of these PIs vs. Kaletra, which had been the only *preferred* first line PI. These studies show that each of these PIs are fairly closely equal to Kaletra (the technical term for these studies is *non-inferiority*) for people taking HIV drugs for the first time. Boosted Invirase was not put in the preferred category because these data, from the GEMINI study, were still preliminary and not yet published in a peer-reviewed journal.

Unboosted Lexiva and Reyataz, along with once daily Kaletra and once daily Lexiva were also added to the *alternative* category. The data on these regimens are not quite as strong as for those in the *preferred* category. However, people may choose those to avoid Norvir, or for more convenient dosing.

Unboosted Invirase, Viracept (nelfinavir), Aptivus (tipranavir) and Prezista (darunavir) are not recommended for first line treatment. It is possible that this will change for Prezista as preliminary data from a head-to-head study vs. Kaletra for first line treatment has shown promising results. The guidelines point out that these data are preliminary, and the dose being studied is not commercially available.

Sustiva (efavirenz) remains the sole *preferred* NNRTI for first line use. Viramune (nevirapine) is listed as an *alternative* option, largely due to concerns over liver toxicity. Rescriptor (delavirdine) and Intelence (etravirine) are not recommended for first line treatment.

Several other drugs are not recommended for first line treatment. In most cases, not including the integrase inhibitor Isentress (raltegravir) and fusion inhibitor Fuzeon (enfuvirtide) is due simply to

a lack of data for the drugs used in this way. In the case of the entry inhibitor Selzentry (maraviroc), it was due to results from a head-to-head study vs. Sustiva, where Selzentry failed to prove as good as Sustiva.

The overall affect of these changes is that people have more options for constructing their first HIV drug regimens. This is good news for people living with HIV. More options mean a better chance to construct a well studied regimen that fits a person's unique needs. More changes might be forthcoming, as companies continue to study their drugs against those in wide use for first line treatment.

Treatment experienced

The section on treatment for people with extensive experience taking HIV drugs dose not include a simple chart of *recommended*, *alternative* and *not recommended* drugs. Treatment decisions for this group are more complex and must be guided by treatment history, resistance testing and other factors.

Several important changes were included in this update. The first is information on the newly approved drugs Intelence, Isentress, Prezista and Selzentry. All of these have been extensively studied in treatment experienced people. The guidelines include a summary of what is known about each of these new drugs, including some data from studies.

A second change was subtle but significant — strengthening the 'treatment goals' section to include language on undetectability and avoidance of serial monotherapy. The goal of reducing anyone's HIV levels to below the limit of detection has always been there. Now the availability of multiple new, potent drugs that when used in combinations are likely to get almost anyone's HIV levels to undetectable. For years, only one new drug became available at a time. This meant that people with few or no treatment options were forced to take each new drug as it became available, often as the only fully active drug in their regimen — a situation called *serial monotherapy*. The approval of four potent new drugs, all either from new classes or able to overcome resistance to older drugs has given almost everyone a window of opportunity to combine multiple new, fully active drugs and hopefully reduce their HIV levels to undetectable.

New language was added on the potential for 'simplification', or reducing the number of drugs a treatment experienced person is taking, when they are on a suppressive regimen. For many years, the approach to treating people with multi drug resistant HIV was to treat with as many drugs as could be tolerated, sometimes called the kitchen sink approach. Some research has shown that when treatment experienced people are on stable suppressive regimens, they can sometimes safely reduce the number of drugs in their regimen — to reduce the risk of side effects and improve quality of life.

Third, more information was added about the risks of treatment interruptions, flowing mostly from SMART, but including other studies like DART, PART and TRIVICAN. The bulk of the data on treatment interruptions show them to be risky. This is especially true for people who have ever had an AIDS-defining illness or CD4 count below 200. Recent data presented at CROI reinforces the growing unease with treatment interruptions.

Other changes

The guidelines changed some of the language around diagnosing and treating acute HIV infection. There is a growing body of evidence on the importance of this earliest phase of HIV disease. It is thought that people in the acute phase of HIV infection — when their immune systems have not yet mounted a full response — are at a particularly high risk of passing HIV onto others. For one thing, people are very likely to be unaware of their HIV status at this point, and therefore may be

less likely to practice safer sex and drug use practices. Some evidence also shows that some of the things that happen during the acute phase, like HIV's invasion into the gut, may predict a person's long-term outcomes. The guidelines added language to help physicians identify people who might be in acute HIV infection, and stressed the importance of testing for NNRTI drug resistance which is more commonly transmitted than other kinds of resistance.

Several changes were also made to the section on treatment for people co-infected with *Mycobacterium tuberculosis* or TB. TB remains a common co-infection for people living with HIV, especially those in jail or who are homeless or living in shelters or other crowded situations. There is a growing problem with multi-drug and extensively drug resistant TB as well. The guidelines added recommendations on treating active and latent TB, as well as drug sensitive and drug resistant TB.

Discussion

The Guidelines are meant to help HIV treating physicians better manage care and treatment decisions. The document is under constant review by a dedicated volunteer group. The panel strives to incorporate the best evidence in an ongoing fashion. The stronger the evidence, the stronger the recommendations.

Sometimes changes in the guidelines can appear to lag behind the cutting edge. This is sometimes due to simple time constraints. Other times, it has to do with strength of evidence. The process of reviewing and updating the guidelines is both fascinating and daunting. The large number of drugs and the many studies of their use require constant vigilance by panel members.

No set of guidelines, however well researched or debated, can ever replace the clinical insight of an HIV experienced clinician. One of the main audiences for the guidelines is treating physicians who do not specialize in HIV, or who only treat a small number of people living with HIV. The guidelines are just a tool to help physicians and people living with HIV make better decisions around their care and treatment. It is a living document, undergoing constant scrutiny and revision.

Currently, four community members are included in the panel to ensure that the user's perspective is always part of the discussions. Paul Dalton, Project Inform's Director of Treatment Information and Advocacy, is a community member of guidelines panel and is the author of this article. This article was not written on behalf of the Guidelines Panel. The entire document can be found at <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>.

Update from CROI 2008 on approved HIV drugs

by Paul Dalton, Director of Treatment Information & Advocacy

The Conference on Retroviruses and Opportunistic Infections is the most important annual science conference in the US covering HIV/AIDS. This year's meeting was held in Boston, MA and included presentations ranging from vaccines to microbicides and experimental HIV drugs to opportunistic infections. This article reviews the research on approved anti-HIV drugs presented at CROI 2008.

SWEET

A poster presentation showed that people switching from Combivir (zidovudine + lamivudine) to Truvada (tenofovir + emtricitabine), experienced increases in limb fat and no changes in HIV levels, kidney function and bone mass. The SWEET study looked at 234 people on stable regimens of Sustiva (efavirenz) + Combivir. Half were randomly assigned to switch from Combivir to Truvada and half stayed on Combivir. Participants were given DEXA scans, which measure bone and fat.

After 48 weeks, people who had switched to Truvada gained an average of 0.2Kg (0.4lbs.) of limb fat, while those who stayed on Combivir had lost a bit less than 0.2Kg (0.4lbs.) on average. The effects were greatest in people who had taken AZT for less than 3 years, and with less limb fat at baseline. There have been concerns with Truvada over kidney function and bone loss. In both cases there were trends toward more problems with Truvada compared to Combivir, but they were not significant.

These results confirm what has been known for some time. Combivir, which was the first fixed-dose combination pill, has a higher risk of limb fat loss than Truvada. This switch study showed that the loss of fat on Combivir could be somewhat reversed with a switch to Truvada. While there were no significant differences between the groups on measures of bone or kidney health, there were small trends that tend to confirm concerns about Truvada.

HEAT

Another poster presented at CROI found that that Epzicom (abacavir + lamivudine) and Truvada performed equally well when combined with the boosted protease inhibitor, Kaletra (lopinavir + ritonavir). This head-to-head study, called HEAT, is important because there aren't much direct comparison data between Epzicom and Truvada — the two preferred fixed-dose combination NRTIs by current Federal Guidelines.

HEAT looked at around 700 people who had never taken HIV drugs, who were randomly selected to take either Epzicom or Truvada alongside Kaletra. About half the volunteers were white and 82% were male. The primary outcome was the proportion of people with HIV levels below 50 copies/ml after 48 weeks. Data were also collected on adverse events and changes in CD4 counts.

After 48 weeks, similar percentages (68% for Epzicom vs. 67% for Truvada) of people in both groups had undetectable HIV. People taking Epzicom had slightly larger increases in CD4 counts (201 vs. 179 cells), but not to a clinically significant degree. There were also similar levels of adverse events among the two groups, with more kidney problems among people taking Truvada and more hypersensitivity reactions in people taking Epzicom.

The current Federal Guidelines, released in late January 2008, list both Truvada and Epzicom as preferred options for first line treatment. To date there has been little direct comparison data to help people choose between these two options. The results from HEAT suggest that either fixed-dose combination is likely to work well, at least when paired with once daily Kaletra.

There are a couple of secondary, but important, notes about this study. First, it used once daily Kaletra, rather than the more widely used and better supported twice daily schedule. This might explain the higher levels of resistance to NRTIs than is typically seen in clinical studies. Also, HLA testing — which fairly accurately predicts the risk of abacavir HSR — was not used. Other studies, like PREDICT and SHAPE, suggest if it were used, a much lower rate of abacavir HSR would likely have occurred.

Lastly, this study only compared these fixed-dose combinations when paired with Kaletra. While Kaletra is a widely used first line option, there are others — notably Sustiva (efavirenz) and Reyataz (atazanavir) — that are common choices for first line therapy. It would be a mistake to apply the results from this study to other drug combinations.

This is an important study nonetheless. The best way to compare drugs is in these kinds of head-to-head studies. The results from HEAT presented here suggest that, along with HLA testing, Epzicom is a reasonable alternative to Truvada, when either is taken with Kaletra.

D:A:D

Another poster presented at CROI found a higher risk of heart attack (*myocardial infarction*) in people using the HIV drugs Ziagen (abacavir, and fixed-dose combination pills Epzicom and Trizivir) and Videx/Videx EC (didanosine, ddI).

These findings came from an analysis from the *Data Collection on Adverse Events of Anti-HIV Drugs*, or D:A:D study. D:A:D is a multi-center study that follows several groups of people, mostly in Europe, and examines the unintended side effects of HIV drugs. Earlier research from D:A:D found that HIV drugs on their own increased a person's risk of heart attack by 26%. The study has also reported on a higher risk related to taking HIV drugs from a specific class — protease inhibitors.

This study examined whether another class of HIV drugs, called NRTIs, also affected the risk of heart attacks. Of the five drugs studied, D:A:D found a significant increase in the risk of heart attacks in people using Ziagen (90%) or Videx (49%), but not Retrovir (zidovudine, AZT), Epivir (lamivudine, 3TC) or Zerit (stavudine, d4T).

Interestingly, the study found that the higher risk was only present when people took the drugs — that is, the risk was largely reversed when people stopped taking them. This contrasts to the protease inhibitors, where the damage grows over time and is not quickly reversed.

The *absolute risk* of heart disease (meaning the likelihood a person is to be diagnosed with heart disease) was strongly associated with known risk factors for heart disease. The effects of Ziagen and Videx were present in people regardless of their absolute risk of heart disease, but they were most pronounced in people at the highest underlying risk of heart disease.

There is no known mechanism that explains this NRTI finding. Protease inhibitors are known to increase cholesterol and the risk of diabetes — both risk factors for heart disease. However, no such affect was seen with these two NRTIs. The fact that the risk disappeared when people stopped the drugs strongly suggests a direct causal relationship between these two NRTIs and the risk of heart disease. More research is needed to understand the mechanism.

It's important to emphasize that the overall rate of heart attacks seen in this study were small. This report does not mean that people on Ziagen or Videx should necessarily stop taking their drugs or switch to others. If you take either drug and you have heart disease or are at high risk for it — due to family history, smoking or other known risk factors — discuss these findings with your doctor.

Viramune once a day

A poster presented at CROI found that Viramune (nevirapine) given once a day was as safe as when given twice a day for people on stable twice-a-day regimens with Viramune. This study looked at just over 300 people in Spain who had been on twice-a-day Viramune regimens for at least 8 weeks (12 weeks for women with CD4 counts above 250), undetectable levels of HIV, and no signs of liver trouble. Half were randomly assigned to switch to once-a-day Viramune, and half stayed on twice-a-day regimens.

Overall there were low levels of liver problems in the study. More cases of liver problems occurred among people taking Viramune once a day, but the difference was mostly due to people with viral hepatitis. There were no significant differences between the groups in terms of maintaining undetectable HIV.

Viramune is the second most widely used NNRTI, lagging well behind Sustiva (efavirenz). The biggest concern with Viramune is the risk of catastrophic liver toxicity, especially in women and people with higher CD4 counts. Viramune is approved for twice-a-day use, but has been widely used once a day because of its ability to stay in the body for a long time. This study suggests that people who are already taking Viramune successfully — meaning they have undetectable HIV and no signs of liver problems — can take it either once or twice a day.

CASTLE

Results from a large head-to-head study of the Norvir (ritonavir) boosted protease inhibitors — Reyataz (atazanavir) vs. Kaletra (lopinavir) — were presented at CROI. For people taking HIV drugs for the first time, the CASTLE study found that Reyataz once a day was comparable to Kaletra twice a day, when each is taken with Truvada.

CASTLE enrolled almost 900 people who were randomly assigned to take either 300mg Reyataz + 100mg Norvir once a day or 400mg Kaletra + 100mg Norvir twice a day. Both groups also took one tablet of Truvada (300mg tenofovir + 200mg emtricitabine) once a day. Researchers compared these regimens in terms of lower HIV levels, higher CD4 counts, and various measures of fat metabolism.

After 48 weeks, similar numbers of people in both groups had HIV levels below 50 copies (78% for Reyataz vs. 76% for Kaletra). People on Kaletra had slightly larger gains in CD4 counts (219 vs. 203), though it's not clinically significant. The most significant difference between the regimens was in side effects. More people on Reyataz had higher levels of *bilirubin* (a protein produced by the liver) and jaundice. People on Kaletra had higher average levels of cholesterol and triglycerides.

This study confirms the growing body of evidence that most, though not all, boosted protease inhibitor regimens perform about the same in lowering HIV levels and raising CD4 counts. The most important differences are found in side effects, drug interactions and convenience. While Kaletra enjoyed a period alone at the top of the hill, the field is now quite crowded, which is a good thing for people with HIV who now have more choices for boosted protease inhibitor regimens than ever before.

Kaletra once a day

A poster at CROI found that once-a-day Kaletra is similar to twice-a-day Kaletra, using the new tablet formulation. This contrasts to earlier research that showed higher rates of treatment failure with once-a-day Kaletra, using the older capsule formulation.

The study, titled MO5-730, began as a four-arm study of 664 people randomly assigned to take either formulation (capsule or tablet) of Kaletra, once or twice a day. Everyone in the study also took Truvada. After 8 weeks everyone taking the older capsule formulation was switched to the newer tablet.

The poster presented data on efficacy and tolerability after 48 weeks. Overall, people in both arms were equally likely to have HIV levels below 50. There was also no difference seen when dividing the groups into people with pre-treatment HIV levels above or below 100,000 copies. There were also no significant differences seen in rates of side effects, which differs from some studies using the capsule once a day. Similar changes in cholesterol and triglycerides were seen in both groups as well.

Resistance testing was done on 17 people who experienced treatment failure during the study: 10 in the once-a-day group and 7 in the twice-a-day. Nobody had developed primary resistance mutations that have been linked to resistance to Kaletra and Viread. Three people developed the M184V mutation strongly linked to resistance to Emtriva.

Selzentry

Further results from the pivotal studies of the recently approved CCR5 antagonist Selzentry (maraviroc) were presented in an oral presentation and poster at CROI. Project Inform has written extensively on the development of Selzentry, especially in the past two years as the drug moved closer to FDA approval. Results presented at CROI (see coverage in *PI Perspective #44*) confirm earlier research but also leave important questions open about this new drug.

As reported on Project Inform's website (www.projectinform.org/news/07_ias/072507b.shtml), the first set of results for the MERIT studies, which compared Selzentry to Sustiva both combined with Truvada in people taking HIV drugs for the first time, were presented last summer at the IAS meeting. Overall, Selzentry didn't quite match up to Sustiva, using pre-defined criteria. Surprisingly, the difference between the drugs was only seen in people in the southern hemisphere.

In an oral presentation at CROI, further analysis was presented of treatment failure in the MERIT trial. In MERIT more people stopped Selzentry due to treatment failure (11.9% vs. 4.2%) than Sustiva. This study sought to explain what caused these treatment failures. Several explanations were presented. In some cases (3.3%) participants' HIV shifted from R5-only to dual/mixed between the time they were screened and started taking Selzentry. Among people who failed on Selzentry who had R5-only HIV when they started taking drug, about one-third had X4-using HIV emerge. This also led them to develop resistance to the NRTI drugs they were taking. Among people who failed while still having R5-only HIV, resistance to Selzentry was detected in only a small number, while most had developed resistance to their NRTIs.

These results raise further questions about using Selzentry in people taking HIV drugs for the first time. One issue is the reliability of the Trofile test — the only widely used test to determine whether a person's HIV is only R5 or can use X4. A small, but significant group of people had different results in the short time between screening and taking their first dose. This issue is important because it takes three or more weeks to get the results of the Trofile test back.

However, the biggest problem is the higher rates of treatment failure compared to Sustiva, which is widely used in as first line treatment. While it is true that more people stopped taking Sustiva due to intolerance in this study, the treatment failures experienced by people in taking Selzentry often led them to develop resistance to other drugs in their combination, therefore limiting future treatment options.

A poster presentation covered both efficacy and safety after 48 weeks of Selzentry compared to placebo, both combined with optimized background therapy in people with experience taking HIV drugs in the MOTIVATE studies. This poster basically confirmed earlier results. About half the people taking Selzentry had HIV levels below 50 copies after 48 weeks, compared to 22% of people taking a placebo. There was a significant difference in responses between people with pre-treatment HIV levels above vs. below 100,000 copies. For people with high pre-treatment HIV levels, only around 35% had undetectable HIV levels, compared to almost 60% of people with lower pre-treatment levels.

There were no significant differences in rates of side effects between people taking Selzentry or placebo. This is important to emphasize, because there has been a high degree of concern over toxicity with this class of drugs. So far, it hasn't been confirmed in studies of Selzentry.

The best use of Selzentry is still unclear. It has not performed as well as some other recently developed drugs when used in treatment experienced people, but it has shown some significant benefit for a subset these folks. Many think that CCR5 drugs are better used earlier, when a higher proportion of people are likely to have R5-only HIV, but the head-to-head studies against Sustiva have raised almost as many questions as it has answered. Further muddying the waters are the concerns over the accuracy, turnaround time and cost of the Trofile test needed to use Selzentry.

Another study was presented comparing changes in lipids in MERIT. On average people taking Selzentry experienced less increases in blood fats, compared to people taking Sustiva. Sustiva has been associated with changes in lipids for some time, so this finding was not surprising.

Wrap up

With the pace of new HIV drug development slowing, research on approved HIV drugs becomes more important. While there were few headline grabbing stories on approved HIV drugs at CROI 2008, each piece of research deepens our understanding of these drugs. More head-to-head and strategy studies are needed to better understand when and how best to use HIV drugs. Alongside our efforts to promote research on experimental HIV drugs and an outright cure, Project Inform advocates for more of this kind of research to improve the treatment of HIV/AIDS.

Update from CROI 2008 on experimental HIV drugs

by Paul Dalton, Director of Treatment Information & Advocacy

Compared to the recent fast pace of new HIV drug development, the next couple of years look relatively quiet. In just over two years 5 new drugs were approved by the FDA, including ones from two new classes. While most people — including those with extensive treatment experience — are now able to build potent regimens, there remains a need for new drugs.

The Conference on Retroviruses and Opportunistic Infections (CROI) held recently in Boston, MA is the most important annual HIV science conference in the US. This article reviews some of the presentation on experimental HIV drugs at this year's meeting.

Vicriviroc (Schering-D)

Data were presented from a study called VICTOR-E1, looking at the CCR5 antagonist vicriviroc in people with experience taking HIV drugs. While generally positive the results raise further questions about this drug's future.

The study compared two doses of vicriviroc (20 and 30mg, both once daily) to placebo, each combined with the best available background regimen in people with extensive experience taking HIV drugs. The study was relatively small, with about 40 people in each of the three groups.

After 48 weeks, about half the people taking either dose of vicriviroc had HIV levels below 50 copies/mL, compared to 14% taking placebo. Average decline in viral loads were greater for people

on vicriviroc as well: 1.77 and 1.75 logs for the vicriviroc groups vs. 0.7 logs for placebo. Vicriviroc was generally well tolerated with few people stopping due to side effects.

While these results suggest fairly potent anti-HIV activity for vicriviroc, further analysis raises significant questions. People with high HIV levels—defined as above 100,000 copies/mL—at the beginning of the study were very unlikely to get to below 50 copies/mL (33% for the 30mg group, 17% for the 20mg group, and 10% for the placebo group). Also, many more people taking vicriviroc than placebo were also taking the protease inhibitor Prezista (darunavir) as part of their background regimen. At the very least this confounds any positive results seen in this study.

There were a couple of other presentations on vicriviroc, including two that looked at resistance and one that found no effect of vicriviroc on HCV. A couple of years ago vicriviroc was locked in a head-to-head race with two other drugs, GSK's aplaviroc and Pfizer's Selzentry (maraviroc), to become the first CCR5 drug approved by the FDA. Aplaviroc's development was halted due to rare, but serious liver toxicity. Selzentry was approved a few months ago. The results presented at CROI are generally positive, but do little to overcome the perception that this once promising drug's uncertain future. The company has chosen the 30mg dose for future development.

Other CCR5 antagonists

There were a couple of presentations on other experimental CCR5 drugs at CROI. Other than vicriviroc, the drug furthest along in development is INCB9471. Data were presented on a 14-day study of multiple doses of the drug compared to placebo in people with R5-only HIV. Overall 49 people were studied, with 9 given a placebo and the rest one of three doses of INCB9471 (100, 200 and 300mg, once daily). No data were presented on reductions in HIV levels or changes in CD4 count. Instead they presented data on people who had X4 HIV emerge during the study. As seen with studies of other R5 drugs, most of the emergence of X4 on these drugs seems to be from a minority population of dual/mixed HIV that was not detected at the start of the study. This highlights the need for better screening tests for R5.

Another experimental R5 drug, called PF-232798, was tested against HIV that had grown resistant to Selzentry. The researchers grew HIV in a lab that was resistant to Selzentry and tested PF-232798 against it. While the activity of PF-232798 dropped off somewhat compared to against non-resistant HIV, it retained sufficient activity to move the drug forward in clinical development.

All of the currently tested CCR5 drugs work by attaching to the R5 protein in such a way that HIV has a difficult time attaching to it. While this strategy can be effective, HIV can develop resistance to these drugs by changing the way it attaches to R5. At CROI, researchers presented early research on another approach to blocking R5 — using a drug to force R5 to move out of the cell membrane to inside the cell. This approach, if proven safe and effective should be less susceptible to resistance. Researchers tested a large number of compounds for their ability to internalize CCR5. They found one, called ESN-196, that they think warrants further testing as an R5 blocker.

NNRTIs

Several new non-nucleoside reverse transcriptase inhibitors are in pre-clinical development. UK-452,061 is being developed by Pfizer. A poster presentation detailed an experiment where UK-452,061 was tested against HIV taken from people who had developed resistance to approved NNRTIs. In all they looked at 62 samples of NNRTI-resistant HIV, and the compound showed good activity against 61 of them. The tests were done in a laboratory, not in people.

Another experiment reported in a poster compared resistance to the experimental NNRTI, IDX899, to the widely used NNRTI Sustiva (efavirenz). In this study, researchers exposed a laboratory strain of HIV to different concentrations of both drugs to try and force resistant HIV to emerge. This type of experiment is done commonly in early drug development. The researchers reported that resistance to IDX899 emerged more slowly compared to Sustiva and neither drug appears to be highly cross-resistant.

Still another experiment looked at two experimental NNRTIs — RDEA427 and RDEA640 — compared to Sustiva against HIV with the most common NNRTI mutations. Both experimental drugs worked better than Sustiva. This is not surprising as the HIV tested would be expected to be highly resistant to Sustiva.

They also tested these two along with another experimental NNRTI, RDEA860, to see how affected they are by human proteins. The extent to which drugs attach to human proteins has a profound affect on how easily therapeutic levels of the drug can be achieved. While each of the drugs was significantly affected by protein binding, they were less so than Sustiva, Intelence (etravirine) or rilpivavirine (TMC-278).

Bevirimat

Bevirimat is an experimental maturation inhibitor being developed by Panacos. Maturation inhibitors work at the same step in HIV's replication cycle as protease inhibitors, but in a different way. Its development has been slowed by problems with formulating the drug. The drug is currently in Phase IIb.

Two poster presentations looked at the development of resistance to bevirimat. One found that protease inhibitor resistant HIV may be less likely than wild type HIV to have resistance to bevirimat. This is a potentially important finding, because bevirimat is being developed for people with extensive HIV treatment experience, who are likely to have HIV that is resistant to PIs. The other study identified several mutations that reduced bevirimat's activity. As the drug moves closer to possible approval, this information will help researchers, regulators and activists as we evaluate the results from clinical studies.

Other drugs

A poster presented at CROI suggests that GS-9148, an experimental NRTI being developed by Gilead, might cause fewer kidney problems than Viread (tenofovir) and might have very good penetration into lymph nodes.

GS-9148 is a *nucleotide* reverse transcriptase inhibitor (NtRTI). Other NtRTIs, including Viread, didanosine and abacavir, have caused kidney damage. This poster showed data looking at GS-9148's affect on kidney cells, from both laboratory and animal studies. Compared to other NtRTIs, little of GS-9148 was taken up into kidney cells. This suggests it is less likely to harm those cells.

Gilead is also looking at how well GS-9148 gets into lymph node cells. Lymph nodes are a major site of HIV replication, and most HIV drugs fail to penetrate well into this important area of the immune system.

The NRTI class of drugs has lagged in development for some years now. As a class they have been hampered by relatively low potency and high toxicity. A new NRTI with low toxicity would be welcome, if it is shown to reduce HIV levels well. More research will be needed to see if the promise of this new NRTI can be achieved.

A poster presented at CROI shows potential for another experimental NRTI, apricitabine. The results were from the AVX-201 study, which Project Inform reported about earlier (see *PI Perspective #44*). AVX-201 compared apricitabine to Epivir (lamivudine, 3TC) in people with HIV that harbors the M184V mutation, which is associated with resistance to Epivir and Emtriva (emtricitabine, FTC).

In the first phase of the study, people on failing Epivir regimens were randomly assigned to either stay on Epivir or switch to apricitabine. After 21 days everyone was switched to a background regimen made up of the best available HIV drugs. Results from this second phase were presented at CROI.

After 24 weeks there was a trend toward better outcomes for people taking apricitabine, but the difference wasn't significant. The authors speculated that the potency of the background regimens and the small number of people in the study made this difference too small to be considered significant. There were more treatment related side effects among people taking apricitabine than Epivir. This is not surprising as everyone in the study had experience taking Epivir.

The development course for apricitabine is unclear. Many people have developed resistance to either Epivir or Emtriva, so a viable option for them is needed. Avexa, the developer of apricitabine, will need to show that its drug is potent and well tolerated in larger trials before we will know if it can be that option.

GlaxoSmithKline and Shianogi presented resistance data on a potential integrase inhibitor, called S/GSK364735. Unfortunately this drug appears to have similar resistance patterns as both Isentress (raltegravir) and Gilead's elvitegravir. However, development of this drug is expected to move forward.

In addition to more traditional approaches to HIV therapy, there's quite a bit of interest in testing anti-inflammatory drugs for activity against HIV. One drug, called Aprepitant which is approved for use against nausea caused by cancer chemotherapy, was tested against a broad range of HIV types. The researchers found potent activity against HIV, with little evidence of damage to cells. The fact that this drug is already approved for people with cancer makes it easier to study in people with HIV, as there is already enough data on its use in humans to believe it is safe. While much more study will be needed to know if this could be an effective approach against HIV, the approach of examining approved drugs against HIV should be examined further.

Final thoughts

Compared to the last couple of meetings, there wasn't a lot to be truly excited about for experimental HIV drugs at CROI 2008. While the recent flood of new and important drugs is certain to slow for awhile, potentially important new drugs continue to be studied. While some look at the current anti-HIV armamentarium and think it might be sufficient, this is hardly clear. While many of the recently approved drugs have performed quite well in clinical trials, long-term, real-world use will tell the full story. New and better drugs — probably many of them — are still needed. Project Inform continues to work to ensure that these compounds are studied and, when warranted, developed.

Update from CROI 2008 on HIV-related infections and conditions

by Alan McCord, Manager of Treatment Information

This year at CROI, many studies covered a variety of topics related to HIV-related infections and conditions, such as tuberculosis, herpes and hepatitis. Some revealed modest advances, some exposed sobering news, while others provided us with a better understanding of how treating some infections impact HIV therapy. Some studies report possible advances in diagnostic tools that could better manage these infections and improve the lives of people living with HIV.

New information on abacavir sensitivity

A serious condition called hypersensitivity reaction (HSR) can occur in 5–8% of people who take the HIV drug Ziagen (abacavir). [Abacavir is also found in the fixed-dose combination pills Epzicom (3TC + abacavir) and Trizivir (AZT + 3TC + abacavir).] Symptoms can appear within 2–6 weeks of taking it. They include fever, rash, headaches, upset stomach, tiredness, sore throat, cough and shortness of breath. They usually get worse over time and can be life-threatening, especially if a person stops and then restarts taking abacavir.

Finding a way to predict who would most likely develop abacavir HSR has the potential to greatly reduce the rate of this condition. Researchers found that people with the gene pair called HLA-B*5701 are more likely to develop abacavir HSR. The HLA test was developed several years ago to screen people before they started a regimen with abacavir. Two studies at CROI reported new information on abacavir HSR.

Study 1

The first study looked at using another gene associated with HLA to predict HSR, called HCP5-SNP. The research followed 108 people in the Swiss HIV Cohort Study who had stopped Ziagen due to possible HSR. A random sample of another 259 who already had HLA test results was also included. The study tested both HLA and HCP5 and then compared the results.

The study showed that all of those who carried HLA also carried NCP5. Only 1% of those who didn't carry HLA had NCP5. Therefore, using NCP5-SNP found everyone with HLA and was absent in 99% of those without HLA. Using NCP5 may lead the way to a simpler and cheaper screening test for people with HIV.

Study 2

Several studies have shown that HLA-B*5701 is greatly associated with abacavir HSR. However, people who could take abacavir safely have not been defined. The second study looked at trying to identify genes that would predict who could tolerate abacavir.

The research followed 95 volunteers with abacavir HSR from three studies, 40 of whom didn't have symptoms of HSR. The study measured the HLA gene and several gene markers related to abacavir metabolism in order to predict the likelihood of HSR. While one genetic variation was found to have a possible relationship to HSR, the authors concluded that the observed relationship wasn't strong enough to warrant more research.

Although HLA testing and perhaps now NCP5 testing are good markers for predicting abacavir HSR, they cannot predict every person who will develop the condition. People who start abacavir, even though they are negative for HLA or NCP5, should still be aware of any symptoms within the first six weeks of taking the drug and report them to their doctors as soon as possible. Put another way, genetic testing for HSR should augment, and not replace, clinical vigilance.

Bone loss increasingly an issue for people taking HIV drugs

As people living with HIV take therapy over time, a growing list of conditions often become important, including bone problems. Research continues to examine the relationship between HIV and bone problems, including bone density loss (*osteopenia*), bone loss (*osteoporosis*), and bone death (*osteonecrosis*). Several studies reported findings at CROI 2008. Though they pointed to some general observations, they have not found the exact cause(s) for the higher rate of bone loss in people with HIV.

One study looked at two different regimens: Kaletra (lopinavir + ritonavir) or Sustiva (efavirenz) taken with Combivir (Retrovir/zidovudine + Efavir/lamivudine) for 24–48 weeks. People were then switched to Kaletra monotherapy through to 96 weeks. The results showed that loss of bone density occurred at about the same rate, suggesting that bone loss occurs independently of the HIV drugs used.

A second study seems to confirm these results. A sub-study of Hippocampe-ANRS 121 followed 71 people over 48 weeks and checked the bone density in the hip and spine. Three regimens that included three different classes of HIV drugs were used. The results showed that all three groups showed bone loss, suggesting again that HIV or HIV treatment contributes to the loss of bone density in people on HIV therapy.

Other studies showed the same types of risks for bone loss that HIV-negative people face, such as older age, low body mass, low activity level and poor nutrition. Risk factors unique to people with HIV include low CD4+ count, younger age than HIV-negative people, and low testosterone levels often found in HIV-positive men.

Nearly 2 in 3 people with HIV show signs of osteopenia. About 1 in 5 has osteoporosis. No standards of care have been established, such as how often to test for bone loss. So more study is necessary to find out the reasons for bone loss in people with HIV and whether and how they pose more of a health concern.

Changes in lifestyle and other strategies shown to prevent bone loss in postmenopausal women can also be used by people with HIV. This includes staying active and getting enough calcium and vitamin D in the diet or through supplements. Other lifestyle changes can also help including stopping smoking, drinking less alcohol and caffeine, and talking to a doctor about medicines that affect bone loss.

Sobering information on genital herpes and HIV

Several studies show that having genital herpes (herpes simplex virus-2, or HSV-2) increases the chance to get HIV by 2–3 times. HIV has a better chance of being passed when there's a genital ulcer present, and HSV-2 is the most common sexual infection that causes genital ulcers. A good deal of research has assessed the relationship of HIV and HSV-2. Several studies reported sobering information at CROI.

The HPTN 039 study followed over 3,000 people and looked at whether using oral acyclovir to control genital herpes would reduce the sexual transmission of HIV. At the start of the study, all tested negative for HIV and 26% of women and 12% of men tested positive for genital herpes. People took either 400mg acyclovir or placebo twice a day. Unfortunately, the results showed that taking acyclovir to control genital herpes did not lower the risk of HIV infection. A smaller study reported similar results last year.

A second study looked at how HIV and HSV-2 interact. Researchers infected human tissues with both viruses in the lab and examined their effects. HSV-2 easily replicated in the tissue while HIV helped in that process. HSV-2 also impaired the production of the cell protein, CCR5, which HIV uses to enter cells. Some think that R5 HIV is less aggressive than HIV that uses another protein, called CXCR4 (X4). These interactions may affect the course of a person's HIV disease.

Since living with both viruses is common in people with HIV, how they interact and to what degree they affect HIV disease is a great concern. These studies not only show how having HSV-2 can affect HIV prevention, they also show that having both viruses may affect the course of HIV disease. These results underscore the importance of people with HIV discussing all health issues with their health providers.

At the least these sobering results may lead to other research, including ones of higher doses of acyclovir, new drugs or combinations of them. At best, they may lead to developing an effective herpes vaccine.

HPV and cervical cancer

At CROI, two studies reported on the types of HPV found in HIV-positive and HIV-negative women in Africa. The first study followed 119 HIV-positive pregnant women and identified 27 distinct HPV types among 72 women. More half the women had high cancer risk types: HPV 58 and 66. Less than 1 in 5 women had the more common cancer risk types, 16 or 18.

In the second study, 200 women were tested for HPV and HIV. Nearly 2 in 3 women had HPV and 1 in 5 women had HIV. The most common high-risk HPV types found were 16, 53, 70 and 81. Women living with HIV were more likely to have other types of HPV, including both high- and low-risk types, than HIV-negative women. They also had a higher number and larger range of types. Not surprisingly, HIV-positive women were more likely to have an abnormal Pap smear.

What these study results show is that women living with HIV may be prone to a larger range of HPV types than HIV-negative women. Though current vaccines provide protection against some types of HPV, new vaccines may be needed to further protect women living with HIV.

What is HPV?

Over 100 types of human papillomavirus (HPV) exist, and more than 40 can be easily passed through genital contact in men and women. Most do not cause symptoms or health problems, increasing a person's chance of passing it onto others. However, some cause genital warts while others cause cervical cancer. Though genital warts can change in shape and size, they do not turn into cancer.

Only one HPV vaccine called Gardasil is currently approved. It protects against two of the most common types that cause up to 70% of cervical cancer: HPV 16 and 18. It also protects against the two types that cause up to 90% of genital warts: HPV 6 and 11. The Gardasil vaccine is recommended for 11- to 12-year-old girls since nearly 3 in 4 new infections in the US occur in 15- to 24-year-old women. However, any woman is at risk throughout a sexually active life.

Another vaccine, Cervarix, is currently being studied in nearly 30,000 women worldwide. This vaccine protects against HPV 16, 18, 31 and 45, which are the four most common causes of cervical cancer.

HPV affects about 20 million men and women in the US. Aside from refraining from sex, the best way to help prevent HPV infection in women is by getting a vaccine, though it will not protect every woman who takes it. There's currently no HPV vaccine for men although it's now being studied.

HIV drugs that penetrate the CNS help control PML

PML, or progressive multifocal leukoencephalopathy, is a rare condition of the brain caused by the JC virus. Before the arrival of potent HIV therapy, a diagnosis of PML disease usually resulted in death within a few months. The one therapy used to treat it, a toxic drug called cytosine arabinoside, is given through a shunt directly into the brain and has shown marginal, if any, benefit. It's no longer routinely used, though some feel that new ways to deliver it should be researched.

As more HIV drugs have been developed during the HAART era, PML is diagnosed less often, and when it is diagnosed the survival rate has improved. This is due to using potent HIV therapy that reinforces a strong immune system which, in turn, keeps PML under control.

It is believed that an HIV protein called Tat helps create more JC virus in the central nervous system (CNS). At CROI, one study looked at which HIV drugs get into the CNS. The results showed that some HIV drugs control PML disease better than others due to their ability to get into the CNS.

HIV drugs with high penetration of the CNS are:

- Crixivan (indinavir) with or without Norvir
- Emtriva (emtricitabine, FTC)
- Kaletra (lopinavir + ritonavir)
- Rescriptor (delavirdine)
- Viramune (nevirapine)
- Retrovir (zidovudine, AZT)
- Ziagen (abacavir)

HIV drugs with moderate penetration are:

Agenerase (amprenavir) + Norvir
 Epivir (lamivudine, 3TC)
 Lexiva (fosamprenavir) + Norvir
 Prezista (darunavir) + Norvir
 Reyataz (atazanavir) + Norvir
 Sustiva (efavirenz)
 Zerit (stavudine, d4T)

HIV drugs with low penetration are:

Agenerase (amprenavir)
 Aptivus (tipranavir) + Norvir
 Fuzeon (enfuvirtide, T20)
 Hivid (zalcitabine, ddC)
 Invirase (saquinavir) with or without Norvir
 Norvir (ritonavir)
 Videx (didanosine, dDI)
 Viracept (nelfinavir)
 Viread (tenofovir)

What this means is that when faced with a diagnosis of PML, using HIV drugs that best penetrate the CNS leads to better survival for the individual. Building or switching to a regimen that includes these HIV drugs may go a long way to improving the health and life of the person faced with PML.

Tuberculosis update

Some people living with HIV encounter an undesirable condition called *Immune Reconstitution Inflammatory Syndrome* (IRIS) after starting therapy for the first time. A similar reaction can also result after starting HIV drugs as the immune system reacts to an already present infection, like tuberculosis (TB), as though it were new. When HIV therapy responds to TB in this way, the condition is called TB-IRIS. About one out of every three cases of IRIS is likely due to TB.

Neither IRIS nor TB-IRIS is well understood, and health providers lack clear definitions of them. This area of research is just now beginning to shed more light on what TB-IRIS means for people with HIV and their health providers. What is not well understood is who is more likely to experience TB-IRIS and what lab tests could be used to predict the condition, among others. Having these answers will better help diagnose, prevent and treat TB-IRIS in people with HIV.

One study presented at CROI examined several markers for their ability to predict who would and would not develop TB-IRIS: IL-12 and serum IL-2, among others. The results reported on 51 adults with TB in Thailand with average CD4 cell counts of 37 before starting HIV therapy. All were diagnosed with various types of TB disease: in the lungs (*pulmonary*), outside the lungs (*extrapulmonary*), and throughout the body (*disseminated*). After starting HIV therapy, 11 developed TB-IRIS within 14 days on average.

Unfortunately these studied markers did not show differences between the two groups, which could be used to better manage TB disease. Although this may sound like a failure, the results will help direct researchers to consider other markers for study. One such study is now looking at other markers, such as regulatory T cells, effector T cells and monocytes/macrophages. The hopeful outcome to this study is the same: to find ways to diagnose, predict and treat possible cases of TB-IRIS.

CROI also provided some update on new drugs in study for treating TB. For more complete coverage on drugs in the TB pipeline, read the article *The Growing Renaissance in TB Drug Study*.

Hepatitis B update

One study at CROI reported on results of how hepatitis B (HBV) affects HIV therapy over time. These areas included HIV levels, CD4 counts, and AIDS-related and non-AIDS-related death. Researchers used a MACS cohort and followed 822 men with HBV taking long-term HIV therapy. The results showed that HBV over time does not alter two markers of HIV therapy: CD4 counts or HIV levels. However, liver-related deaths were higher in those with chronic HBV and non-AIDS deaths were higher in those positive for HBcAb, a marker of HBV disease. These results are similar to what was reported from a South African study. After 72 weeks of HIV therapy in 539 people, no evidence was found that HBV affected the response to HIV treatment.

Two genotypes of HBV — A and D — are the most common ones found in people with HBV alone and HBV/HIV together. One study looked at how both affect use of Epivir (lamivudine, 3TC), a drug that's used to treat both HIV and HBV disease. The study followed 68 people with HBV who took Epivir an average of 41 months. The results showed that the type of HBV heavily influenced different mutations associated with resistance to Epivir. How this affects resistance to other HBV drugs is unknown.

Hepatitis C update

Treating hepatitis C (HCV) disease in people living with HIV can be difficult. Currently, there's no standard of care for when to start HCV therapy in these individuals. It's generally believed, though, that treating HCV should be started when liver function is consistently abnormal. However, more recent data show that treating acute HCV infection early results in better outcomes. About 2 in 3 people who take effective HCV therapy maintain control of their acute HCV, while only about 1 in 3 with chronic HCV are able to control their disease. Several studies at CROI reinforce this, as well as provide other information on managing HCV and HIV disease.

In a very small study, researchers examined the effects of CD4 cells specific to HCV in HIV co-infection. Three people who were infected with both viruses at the same time were treated for both of them early in their co-infections and then followed and compared to a control group. Results showed that treating both infections early in the acute stage helped produce and maintain CD4 cells specific to the HCV infection, which in turn helped control their HCV disease.

A larger study of 150 HIV-positive men with acute HCV infection showed the same results. A total of 111 started HCV therapy: 14 with pegylated interferon and 97 with pegylated interferon + ribavirin. Treatment was started within 6 months of HCV infection and lasted from 23 to 43 weeks. Two out of three sustained control of their HCV infection and no differences were noted among the various types of HCV found in the study.

People living with chronic diseases like HCV and HIV have a higher risk for heart disease. The FRAM study looked at using a marker called C-reactive protein (CRP) to predict the risk of heart disease in people infected with both HIV and HCV. After analysis of 1,135 HIV-positive volunteers, HIV infection alone showed higher CRP levels in men but not in women. For co-infected people, lower CRP levels appeared in both men and women. These data raise the question whether CRP will predict heart disease differently in people with HIV and HIV/HCV. With more study, this marker may be developed to diagnose and help prevent heart disease. A similar result was found in a study of 19,424 co-infected veterans who had statistically significantly more heart attacks due to HCV disease.

The long-term benefits from using HCV therapy in people with chronic hepatitis C have been well established, including a lower risk of liver disease progression and death. However, these benefits in people with both HCV and HIV have not been studied. The GESIDA 3603 Study Group examined the long-term effects of using interferon + ribavirin to treat chronic HCV disease. The volunteers generally had good control of their HIV and all were treated with some form of interferon + ribavirin. Overall, 1 in 3 people sustained good control over their HCV, though that depended upon their type of HCV. Those with types 1 and 4 (14%) had less control of their HCV while those with types 2 and 3 (46%) had better control. Several studies have shown that types 1 and 4 are more difficult to treat.

A few observational studies have suggested that mothers with both HCV and HIV have a higher risk for passing HCV onto their children. In a Spanish study, 631 pregnant women were followed, of whom about 2 in 5 had both infections. Results showed that no cases of both HCV and HIV were passed, while seven transmission cases of HCV were reported. This rate is below what has been reported before.

An Italian study examined the rate of AIDS-defining malignancies in 6,285 HIV-positive people with HBV or HCV infection. The malignancies studied were non-Hodgkin lymphomas and cervical cancer. Of the total volunteers, 38% had HCV and 5% had HBV. The results showed that those living with HIV and HBV or HCV had a higher risk for an AIDS-defining malignancy, especially if cirrhosis had been diagnosed. However, these same individuals were not at higher risk for other AIDS-defining illnesses like herpes or TB.

Hepatitis D

In general, hepatitis is a major concern for people living with HIV. Many live with chronic HBV and/or HCV infection, which can worsen liver health and challenge treatment regimens. Another hepatitis virus, hepatitis D (HDV), can further complicate matters when it's present with HBV or even HBV/HCV.

HDV must use parts of HBV to live and reproduce, specifically the hepatitis B surface antigen, HBsAg. One study reported on using HBsAg as a way to better manage HDV disease. A small study followed 16 people with chronic HDV after starting HIV therapy with either Epivir (lamivudine, 3TC), Viread (tenofovir) or Emtriva (emtricitabine). A significant relation was found between the levels of HDV and HBsAg. Ten of the volunteers showed a decrease between the two levels at the same time. For the other six, no significant change was found despite successfully treating HBV. The study concluded that checking HBsAg levels may be useful in managing HDV disease in some people.

The growing renaissance in TB drug study

by Alan McCord, Manager of Treatment Information

Nearly one-third of the world's population is infected with *Mycobacterium tuberculosis* (TB). Each year, about 9 million develop the active disease and about 2 million die. Globally, it's also the leading cause of death in people with HIV. Over the years, TB has developed resistance to several of the antibacterial drugs used to cure it. World health personnel are scrambling for answers as they now face multi-drug resistant (MDR) and extensively drug resistant (XDR) strains of TB.

Treating standard TB in people living with HIV is difficult, let alone treating MDR-TB. Those with active TB disease must take up to 4 drugs (rifampin, isoniazid, ethambutol and pyrazinamide) and treatment lasts 6 months, often with side effects and often interfering with treating HIV disease. Many do not complete the course of treatment. In many cases, people are given the drugs under the supervision of a health provider, called directly observed therapy, which can tax a person's lifestyle and which is not possible in some communities.

In resource-poor countries, properly treating TB is a great challenge, as health care infrastructures do not exist or are not sufficient. Some areas do not have the medical staff to treat or observe everyone; some encounter poor adherence which results in more resistant TB; and some simply don't have enough drugs.

These, among other reasons, have spurred global interest in developing new drugs for TB as well as using other antibiotics in more effective ways. The current TB drugs date back to the 1960s. Below is hopeful information on the TB drugs now in study. The main goals for developing these new drugs and schedules are to offer a shorter course of treatment, improve adherence, fewer interactions with HIV drugs, and perhaps reduce the pill or dose count.

Rifapentine

This drug was originally studied in 1998 to treat TB, but was found to be less effective than rifampin at its then-studied dose. Its TB use was abandoned, though it is widely available as an antibiotic. Currently, rifapentine is being studied in mice at higher doses and more frequent dosing. So far, results are very encouraging.

A study compared the approved three-drug TB regimen (rifampin, isoniazid and pyrazinamide) to a regimen with rifapentine (in place of rifampin) and moxifloxacin (in place of isoniazid). After two months, the rifapentine regimen showed lung tissue without TB while the standard regimen still showed TB. After three months of treatment, the mice showed no TB relapse on rifapentine. The mice on the standard regimen needed six months of treatment to prevent relapse. Rifapentine appeared well tolerated.

It will take more study in humans to see if the same or similar results occur. With these results, rifapentine may still be potent given three times a week rather than daily, or even given with other drugs like isoniazid in place of the moxifloxacin. So far, using rifapentine shows great promise by potentially cutting in half the time a person with TB would be on therapy. Phase II studies should begin by mid-2008 to gauge its safety and effectiveness.

Moxifloxacin

This antibiotic is in large scale phase III human study. It's already approved for treating other lung conditions. Research hopes to show that as part of a four-drug regimen moxifloxacin will reduce treatment time from six months to four months or less.

Moxifloxacin affects TB in a different way than other first line TB drugs. It also doesn't interact with the P450 liver protein that's used to break down many HIV drugs, which results in fewer drug interactions and side effects.

A current study, called REMoxTB, will use the standard four-drug, six-month treatment against a 4-drug regimen with moxifloxacin instead of ethambutol or isoniazid. Results will be forthcoming.

Gatifloxacin

This antibiotic is used to treat various bacterial infections and has shown fairly good activity against TB in both the lab and in mice. It is believed that gatifloxacin will work well with HIV drugs. Current studies in mice are comparing various regimens of gatifloxacin to the standard TB regimen. The hope is that gatifloxacin could reduce the standard regimen from six months down to four or less.

One study compared two regimens of gatifloxacin to isoniazid. The second regimen (100mg/kg gatifloxacin + 10mg/kg rifampicin) was more effective than rifampicin + isoniazid after 12 weeks. Though TB was not found in lung tissue, the regimen did not reach a durable cure, which means relapse was likely. Another study compared gatifloxacin + ethionamide with or without pyrazinamide. After 12 weeks of therapy, the regimen with all three drugs produced a durable cure, with no relapse within the next 8 weeks.

The role that gatifloxacin plays in treating TB is not well defined from these studies. It appears the drug works against active but not latent TB. This may limit its usefulness for improving the treatment regimens for TB, though it may offer an alternative to TB-resistant drugs like isoniazid or rifampin. More study is needed to see how gatifloxacin fits into TB therapy.

TMC-207

Study of this new antibiotic has shown it has many desired qualities for treating TB. These include potency against drug sensitive and resistant strains of TB; no cross-resistance to other TB drugs; potency against active and latent TB; a long half life making it possible for once weekly dosing, cutting the course of treatment perhaps by half; and low likelihood for drug interactions, which is important for those taking HIV drugs.

Study in mice has shown that TMC-207 is not only potent on its own but especially when used with other TB drugs. In the combination regimens, TMC-207 was as effective within one month as what the standard TB regimen was within two months.

An Irish study has enrolled 60 people and will examine three different doses of TMC-207 compared to two other regimens, one with isoniazid and one with rifampin. The safety and effectiveness of 25mg, 100mg and 400mg TMC-207 once a day will be evaluated over 7 days in people who have never used TB drugs. Results will be forthcoming.

PA-824

This new antibiotic is in phase II study in South Africa. Its novel mechanism shows promise for treating drug sensitive and drug resistant TB as well as active and latent TB. It appears more potent than isoniazid and rifampin. Researchers are hoping to greatly shorten the standard six-month regimen to three months or less, though there are no clear data yet to support this.

Early study using PA-824 in healthy volunteers showed that it's well-tolerated. It does not appear to affect the liver's P450 protein, which reduces possible interactions with HIV drugs. A current study is evaluating its short-term potency by giving volunteers PA-824 only or the standard 4-drug regimen for 14 days. Should the drug prove potent, it will move on to test for safety and effectiveness.

OPC-67683

This new antibiotic is being developed by Japanese researchers, though not much is known about it. What has been reported so far is that OPC-67683 prevents TB from multiplying in the lab and in mice. It has shown to be highly potent against TB and was also able to fight drug resistant strains.

OPC-67683 was used with two approved TB drugs (isoniazid and rifampin) and showed a quicker response than the standard four-drug regimen. So far, the compound does not affect the P450 protein, which is good news for people with HIV. If proven effective in human study, OPC-67683 will likely be taken with other drugs to prevent drug resistance, as will all the other drug candidates in the pipeline.

SQ109

Early lab study shows that this promising new antibiotic contributes good potency when combined with the first line TB drugs isoniazid or rifampicin. It also showed potency against TB resistant to rifampicin. However, SQ109 was not as effective when combined with the other standard drugs, ethambutol or pyrazinamide.

One study in mice compared SQ109 to isoniazid and ethambutol. Results showed that SQ109 is as potent as isoniazid and was superior to ethambutol. Another animal study showed about the same results when using isoniazid and rifampicin with SQ109 instead of ethambutol, with or without pyrazinamide. After 8 weeks, the SQ109 regimen showed significantly lower levels of TB in lung tissue. More study is ongoing.

Macrolides and ketolides

In the late 1990s, research ushered in high hopes for using these types of antibiotics to treat TB. Common examples of macrolide antibiotics are azithromycin, clarithromycin and erythromycin. Although lab research has shown some activity against TB, none of the macrolide candidates has proved more effective than the drugs isoniazid and rifampin. More study is ongoing to create a macrolide that has broader control over TB.

Another type of antibiotic called ketolides has also been suggested for treating TB as they are similar to macrolides. They're currently used to treat respiratory infections that are resistant to macrolides. So far, early study has not been favorable in finding one that is potent against TB.

Pyrrole LL-3858

An Indian company is researching this compound for possible activity against TB. So far, no public information has been made available on it.

Commentary

This renaissance in TB drug study shows a great deal of potential in making regimens shorter, more effective, and with fewer side effects. For people living with HIV and TB, new drugs that don't interact with their HIV regimens are critically needed. Many of these drugs hold promise for them.

Though the world TB epidemic needs new drug solutions today, the soonest that one of them is likely approved may not be until 2010 or 2011. The research process is a difficult one for TB. Clinical study in humans must compare the new drugs against current therapy. Given that the current course of treatment lasts six months and standard time checking for relapse is another two years, TB study takes time to complete.

Although the US does not have as high a level of concern with MDR-TB, better regimens will benefit everyone, especially those countries without the health care infrastructures that are necessary to fully combat this disease. As promising as this research is, much more study still needs to be conducted, especially in people with HIV and other co-infections such as hepatitis C.

Nano comes to HIV

by *Martin Delaney, Founder*

One of the most interesting reports from CROI 2008 described new types of drug delivery using "nano-technology." While scientists have experimented with such approaches for a number of years, presentations at CROI showed that this technology is much closer than previously believed.

Nano-technology offers the possibility of treatments taken only once every few weeks or even once every two months. This would usher in a whole new paradigm of HIV treatment, one that makes even today's "one pill once a day" regimens seem primitive and intrusive. Scientists revealed this approach using a number of different currently available drugs. Still, obstacles remain before anyone can expect to order up an HIV nano-drug at the local pharmacy.

The term *nano* has become part of the language of many areas of science, including biology and drug development. It entered the public consciousness mostly through science fiction, associated with hordes of self-replicating tiny robots that either help or destroy human kind. In the real world, it simply refers to things that are very tiny. Nano is simply a term of measurement, very much like the "centi" in centimeter (one hundredth of a meter). In the simplest terms, *nano* means one-billionth of some measure. Scientists have shown the ability to make tiny but functional mechanisms and processes that operate on the nano scale, including drug delivery.

Tibotec, who already brought two new HIV drugs to market in the last year, revealed an encouraging approach. They have a third drug, rilpivirine (TMC-278), moving toward FDA approval. It was with this drug that they showed their new nano-technology. Rilpivirine is a non-nucleoside reverse transcriptase inhibitors (NNRTI), in the same class as Sustiva (efavirenz) and Intelence (etravirine).

In experiments, they combined the drug with nano-crystals, creating a “nano-solution” which suspends the drug in the blood and particularly in lymph nodes. The HIV drug is released very slowly as the solution breaks down over many months, all the while maintaining adequate levels. So far, the drug in this solution has only been given to 48 HIV-negative volunteers, so its antiviral properties against HIV have yet to be measured. Studies are currently planned.

It is easy to imagine the potential benefits of such an approach. Instead of a daily diet of pills that are processed through the digestive system, a patient would simply get an injection, similar to a flu shot, once every few months, or as seldom as twice a year.

Although the Tibotec experiment used only one HIV drug, there’s no reason that similar technology couldn’t deliver several drugs at the same time. In fact, lab studies are already doing so. In another experiment, researchers at Creighton University in Omaha, NE combined Kaletra (lopinavir + ritonavir) with efavirenz into nano-particles and tested them in lab studies. Results showed that the nano-particles could provide sustained release of the three drugs for at least two weeks from a single dose. Longer release may well be possible.

Other experiments have been reported recently using nano-technology as a delivery mechanism for CCR5 entry inhibitors. There appears to be a great deal of interest in exploiting various forms of nano-technology for the next wave of simplifying therapy in HIV and other diseases.

One important concern with this approach is what might happen if a person has a serious allergic reaction to a drug that has been given this way. With most drugs, allergic reactions begin to lessen as soon as a person stops taking the drug. But when the drug has been given by nano-technology, it’s in the bloodstream for weeks or months to come. However, this is not believed to be a major obstacle. It requires that the manufacturer develop a fast acting antidote or antibody that will destroy or block the activity of the nano-drug. Such an antidote is currently under development for rilpivirine, and it’s safe to assume that any company using this technology will be required to do this.

It is amazing to see how far HIV drug technology has come in the last dozen or so years. When truly effective therapy first became available in 1996, it often required large numbers of pills that were difficult to swallow and had to be taken at least three times a day, often with great quantities of water and with or without food. By 2005 we had one-pill, once-a-day regimens. Now, just a few years later, we are on the can see the possibility of treatment that might be taken as little as a few times a year. Advances like nano-technology are exciting on their own. The speed at which this technology is advancing leads us to ask, can a true cure really be that far away?

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