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

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Twenty-five Years in the Fight Against AIDS: What Have We Learned?

Twenty-five years of fighting HIV and AIDS has taught us many hard lessons, and the learning is far from over. We've learned a great deal about the intersection of epidemics of addiction, violence, poverty and disease as well as the many ways in which politics and prejudice affect what is fundamentally a medical problem. So many have paid with their lives for the lessons learned that it is hard to remind ourselves that society is bettered by the experience. One aspect of the medical fight against HIV that should be carefully studied is what we have learned about confronting a new disease and how it might be applied in the future.

An informative contrast can be found between the 1970's "war on cancer" (generally considered a failure) and the 1980's and 1990's war on AIDS (considered one of the great success stories of modern medicine). Why did one fail and the other succeed? Though the answers are complex (and it's clear that AIDS research itself benefited greatly from the prior assault on cancer), important lessons can be drawn about why the AIDS fight has done so much, at least among those with access to care and modern medicine, to reduce the terrible suffering and death rates seen in the early years. How was this achieved? What does it tell us about fighting other illnesses?

The perceived failure of the War on Cancer left many in the scientific community humbled and the government wedded to the belief that "throwing money" at research for a disease doesn't work. Most scientists came to believe that directing research toward specific goals doesn't speed progress; that advances largely come only from serendipity and encouraging scientists to work on whatever interests them. Time and again, we were told that studying yeast cells was as likely to bring an advance against cancer as studying the cancer itself.

The AIDS experience has in many ways shown exactly the opposite. It has shown that large, consistent long-term funding—directed toward specific objectives and goals in the context of a particular disease—really can pay off. AIDS activists and supporters in Congress and the last three Administrations successfully secured major increases in funding for the National Institutes of Health (NIH). Some of the largest increases went to supporting research against HIV, allowing the NIH and in particular the National Institute of Allergy and Infectious Diseases (NIAID) to lead a full court press against the disease. Importantly,

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these funding levels were either increased or sustained with each passing year for nearly two decades—far longer than support was provided for the War on Cancer.

Leadership within NIAID wisely created a balance of programs that supported basic science about HIV itself, HIV pathogenesis (how HIV causes disease), drug discovery, and clinical testing of new drugs. The funding was spread throughout the country to attract the involvement of our best universities and. The more these groups saw the opportunity for secured long-term funding, working in AIDS became the smart thing to do.

Similar directed funding was used to kick-start the involvement of America's pharmaceutical companies. Federal grants helped identify the basic targets for therapy and supported the screening and testing of new drugs. Within a decade or less, industry had taken the ball and run with it. Smaller and newer firms were seeded with federal grants to do the early work on novel AIDS-related products while the larger companies funded the development of compounds through the costly and time consuming FDA approval process. Today, most HIV drug development is the work of a small cluster of major firms, each heavily invested in developing a full portfolio of products that attack HIV from multiple angles. As treatment has begun to be made more accessible in developing nations, the international generic drug industry has taken on the task to producing less expensive and sometime innovative new versions of existing drugs.

Another key element of the success achieved in treatment has been the unprecedented inclusion of the patient and primary care physician communities into the research process. After years of initial reluctance, patients and their care givers were eventually welcomed into scientific meetings and onto drug company advisory boards. For many years now, every clinical study has been massaged by the patient community, not just institutional review boards and professional groups. This involvement of an aggressive and well informed patient constituency has been widely heralded by scientists and patients alike. Its contrast with the passive community advisory boards of the past couldn't be more stark. Its contribution to progress and understanding cannot be overstated.

Despite the painfully slow start in the Reagan era, steadily increasing funding of AIDS programs at the NIH orchestrated our academic and industrial resources toward achieving long-term goals. Long-term, consistent funding made it possible for academia and private industry to confidently invest in HIV without worrying when or whether the funding would dry up. Opening the doors of academia and private industry to the voices of those affected by the disease has humanized the science and brought it new levels of both support and useful constructive criticism. Collectively, these efforts proved that investing heavily and consistently in the fight against a disease and opening the doors to greater public input does indeed pay off. They showed that science can be guided toward specific goals, albeit with a gentle but wise hand. The key to such wisdom has been to bring all the relevant parties to the table and to continually remind ourselves of the importance of the patients' voices.

These efforts have changed HIV disease from a rapidly progressing, almost always fatal condition to what is today a largely manageable condition, at least for those with access to medical care. In this 25th year of AIDS, we have nearly 25 new drugs that have collectively changed the nature of the disease—an unprecedented rate of new drug development. When people have access to the medicines and medical care, HIV can be held at bay for decades. Though this is not yet a cure, it is a stunning and welcome advance over the suffering that people faced early in the epidemic.

In memory of ...

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

Ron Beauregard
Will Carter
Dan Dunable
Frank Jackson
William Peltier
Ric Weiland

We have also learned the critical importance of combating drug resistance through patient adherence training and developing a constant stream of newer and better drugs, something neither tried nor accomplished very well in any other disease. Developing newer and better drugs continues to this day with at least four or five important new medications nearing approval over the next two years. With each passing year, HIV becomes more manageable, the drugs safer and easier to use, and the development of resistance ever more distant.

If only we could make as much progress against the social, economic and political obstacles faced by people with HIV worldwide. Drug prices, lack of infrastructure, sanitation and medical care, and the callous indifference to the needs of the poor keep many millions from benefiting from these advances. As long as these obstacles remain, these benefits remain out of reach for far too many. We have also failed miserably in the pursuit of prevention, both nationally and internationally. We would not need to struggle so mightily to find the funds to support treatment for tens of millions of people around the world if we had perhaps invested more effectively in prevention along the way. Conversely, had we succeeded in prevention, the cost of treatment would be greatly reduced since fewer people would need treatment in the first place.

We cannot afford to ignore these important lessons. In addition to bringing the success of HIV treatment to the developing world, these lessons should now be applied to the fight against any number of other major illnesses that have not fared as well at the hands of government and science. In the same developing countries so badly in need of access to HIV treatment, millions more die annually from such diseases a tuberculosis, malaria and hepatitis. We cannot go back to serendipity and lower, inconsistent funding levels. We cannot go on under-funding prevention efforts. A vaccine for HIV still tragically eludes us and the vaccine research effort still seems inadequately funded and lacking in leadership. These challenges are as great and as unmet today as they were in the 1980s. Our very success in treatment research and development points the way toward success in prevention: it requires bold, consistent, long-term funding and worldwide collaboration among patients, physicians, researchers, governments and the general public. That is what it took to change the nature of HIV disease through treatment research, and it is what it will take to stop its spread.

Beyond HIV, we face new threats like the bird flu and other less well known pathogens, plus whatever nature will bring us in the future. Thanks to the efforts of scientists, activists, doctors and nurses, the National Institutes of Health, our universities, private industry and supporters in government, we now know a great deal about fighting HIV and any other new disease. The challenge before us now is to apply those lessons worldwide.

International AIDS Conference: Toronto

The 16th International AIDS Conference was held in Toronto, Canada in August 2006. Once a scientific meeting, over the years "big International" has been transformed into a massive, multi-faceted meeting encompassing nearly every aspect of the pandemic—from sessions on reducing HIV stigma, marches in support of sex workers and needle exchange to star power press conferences by Bill Gates and Bill Clinton.

While not the hot bed of breaking science that it used to be, this year's conference had plenty to keep treatment activists busy. Project Inform posted quick breaking news items throughout the meeting, available at *www.projectinform.org/blog.html*. This article is an overview of some of the most interesting and important treatment focused presentations.

Integrase Inhibitors: the next frontier

A few years ago, much of the excitement for new anti-HIV drugs focused on a new class of drugs called entry inhibitors. While there is still interest in these drugs, excitement is shifting to another new type, called integrase inhibitors. Integrase is a type of protein, called an enzyme, which HIV uses to mix its genetic material with a cell's own genes. While drugs targeting HIV's other major enzymes (reverse transcriptase and protease) have been available for years, developing a drug to work against integrase has proven a more daunting task. This appears to be changing, and rapidly.

MK-0518

MK-0518, being developed by Merck, is expected to be the first integrase inhibitor to go before the Food and Drug Administration (FDA) for approval. Merck presented data earlier in 2006 that showed remarkable results using MK-0518 in people who have previously used anti-HIV therapy (called treatment experienced people). There were two important developments related to MK-0518 in Toronto.

First, Merck presented data on MK-0518 use among people on anti-HIV therapy for the first time. They compared MK-0518 to Sustiva (efavirenz), both taken with Epivir (lamivudine, 3TC) and Viread (tenofovir). Similar proportions of people taking MK-0518 and Sustiva achieved undetectable viral loads. After 24 weeks about 80% of both groups had HIV levels below 50 copies.

What drew the attention of treatment activists and researchers was the speed at which people's viral load declined when taking MK-0518. After only four weeks, 60–78% (depending on dose) of people taking MK-0518 had HIV levels below 50 copies, compared to only about 20% of those on Sustiva. Similarly after eight weeks, 75–83% of people on MK-0518 had HIV levels below 50 copies, while only about 37% of people taking Sustiva did. By 24 weeks, however, the effects of the two different regimens were roughly the same, so the striking effect of MK-0518 was how quickly it reduced viral load to undetectable levels. It is too early to fully understand what this rapid reduction in viral load in people taking MK-0518 means. However, earlier studies have suggested a strong connection between how quickly HIV levels drop and how long lasting that response is.

The second development happened on the last day of the conference when Merck announced their plans to open an expanded access program (EAP) for MK-0518 within a few weeks. As Project Inform has written about, U.S. enrollment for the MK-0518 EAP has now opened. To qualify, people must have resistance to at least one drug from the NRTI, NNRTI and PI classes and be unable to fully suppress HIV replication on their current regimen. There is no CD4+ cell count or viral load requirements. For more information, please visit *www.projectinform.org/blog_02_md.html*.

Other Integrase Inhibitors

Two other companies that are developing integrase inhibitors made announcements in Toronto as well. Gilead Sciences reported a lack of drug interactions between their integrase inhibitor, GK-9137 (taken with a booster dose of Norvir [ritonavir]) and their two other anti-HIV drugs, Emtriva (emtricitibine, FTC) and Viread (tenofovir). This bodes well for a possible future fixed-dose combination pill of those three drugs.

GlaxoSmithKline and Shionogi announced completion of their phase I safety study of their joint venture in developing the integrase inhibitor, 364735. No data were presented, but the companies did report that the results allowed them to choose a dose to move forward with for their Phase II study, set to open later in 2006. The companies also announced they will present data from the Phase I study at an 'upcoming medical conference in 2007'.

Others Coming Soon

Integrase inhibitors may be the subject of most of the buzz these days in anti-HIV drug development, but they are not the only ones expected to become available in the near future. The first oral entry inhibitor, a new NNRTI for people with resistance, and possibly one or two other new drugs are on the horizon. For quick notes on all of the experimental anti-HIV drugs in the pipeline, see page 11.

Maraviroc

Maraviroc looks likely to be the first entry inhibitor pill to become widely available to people with HIV. While late 2005 saw a series of setbacks for this new class of anti-HIV drugs, maraviroc continues to move through the clinical studies process. The most interesting data were presented on the final day, during the 'late breaker' session.

Pfizer, developer of maraviroc, studied 186 people with dual tropic HIV—meaning their HIV could use either of two major receptors (CCR5 or CXCR4) in order to enter a cell. (For more information on these receptors, read Project Inform's publication, Understanding HIV: CCR5 and Fusin.) HIV that uses CXCR4 is believed to be more aggressive and disease-causing than HIV that uses CCR5. People who have virus that uses both receptors are thought to be at particular risk for HIV disease progression.

Everyone in the study received what researchers believed was the best possible standard anti-HIV therapy. Additionally, one group was given a placebo and two other groups took one of two doses of maraviroc, given either once or twice daily. The main goal of the study was to see whether people taking maraviroc would experience any harm from blocking CCR5 and theoretically causing the more aggressive CXCR4 virus to dominate.

After 24 weeks, most people responded well to therapy, with no evidence of a harmful effect from blocking CCR5. The placebo group and the group taking maraviroc once daily had almost identical reductions in viral load of .91 log and .97 log respectively. The group on maraviroc twice daily fared a little better with 1.2 log reduction in viral load, but this was not statistically significant. The lack of strong response to maraviroc was somewhat disappointing, but the company was quick to point out that the study was not designed to measure the overall potency of maraviroc.

The one surprising finding was that the groups on maraviroc had larger increases in CD4+ cells (59 and 62 cells) than the placebo group (36 cells). This seems to have allayed fears that using the R5-blocking drug would cause a shift toward HIV that destroyed more CD4+ cells. Why this improved CD4+ response occurred in spite of the lack of a significant improvement in viral suppression over the placebo group is unclear. The numbers of people in studies is relatively small and the period of follow-up was only 24 weeks, so it is premature to say that this question has been fully answered.

Etravirine

Dr. Cal Cohen presented data on Tibotec's second generation non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine (formerly called TMC-125). The study compared two doses of etravirine (400mg and 800mg, both twice a day) together with a potent anti-HIV regimen (optimized background therapy) to a potent regimen that didn't include etravirine.

While most people (39 of 40) taking only the optimized background stopped during the study—mostly due to increases in HIV levels while on therapy—less than 10% of people on regimens with etravirine experienced rebounds in HIV levels. This is a hopeful finding.

Less impressive were the numbers of people able to achieve robust reductions in HIV levels. Among people taking 400mg of etravirine twice daily, only 23% had viral loads below 50 copies after 48 weeks. The higher dose group—800mg of etravirine twice a day—had similar results, with 22% achieving viral suppression to below 50.

Digging a bit deeper it seems that people who had the least evidence of NNRTI resistance (fewer resistance mutations) had the largest drops in viral load. People with a single mutation taking the 800mg dose experienced an impressive 1.67 log reduction in HIV levels, while people with two mutations achieved a drop of 1.38 logs. People with more than three only experienced a modest 0.54 log drop. These results suggest that etravirine will be most useful for people with limited NNRTI experience and of less use for people with NNRTI resistance.

The company has chosen the 800mg twice daily dose with which to move forward. The company expects to file for approval for this drug sometime in 2007. It is available through an EAP now. For more information on the etravirine EAP, please visit *www.projectinform.org/bn/bnews_091106.html.*

For more treatment and health care information, call Project Inform's toll-free National HIV/AIDS Treatment Hotline at 1-800-822-7422.

Deeper in the Pipeline

In addition to the data presented on drugs we expect to see in the next year or so, research on experimental anti-HIV drugs deeper in the pipeline was also presented.

Vicriviroc

Data on another CCR5 inhibitor, called vicriviroc (by Schering-Plough), were presented. Roy Gulick, MD of Cornell University showed data from an AIDS Clinical Trials Group study, ACTG 5211, comparing three doses of vicriviroc (5, 10 and 15mg) to placebo in treatment experienced people. The 5mg arm of the study was stopped early due to poor results. The results for the other groups looked like this:

	10mg Vicriviroc	15mg Vicriviroc	Placebo
Change in viral load at 14 days	-1.15 log	-0.92 log	+0.06 log
Change in viral load at 24 weeks	-1.86 log	-1.68 log	-0.29 log
Change in CD4+ cell count at 24 weeks	+142	+142	-9

These results are encouraging for vicriviroc, but there are concerns as well. There were five cases of cancer among people in the vicriviroc groups compared to two in the placebo group. It is too early to know whether this is due to the drug or just from chance. Project Inform will watch this issue closely.

TNX-355

Robin Hardwicke presented data comparing Tanox' entry inhibitor TNX-355 + optimized background therapy to optimized background therapy alone. Compared to optimized background therapy alone, more people taking TNX-355 were able to reduce viral load by more than 1 log (35% vs. 11%). They also had greater increases in CD4+ cell counts (about 50 cells vs. 1). TNX -355 is a monoclonal antibody that blocks HIV from connecting to CD4+ cells. It is delivered by intravenous infusion twice per month. While IV infusion may seem burdensome, the fact that it is given only twice a month makes it seem more reasonable.

Compared to the results seen lately with Prezista (darunavir) and MK-0518, the results seen with TNX-355 are only modest. However, this represents a new approach to battling HIV (see *Pipeline Update: Short Notes on New Anti-HIV Drugs in Development* on page 11) and in that context, the results are encouraging. Concerns about the way it is given (IV infusion every two weeks) and eventual cost have some activists openly questioning the role of this drug. The data presented here in Toronto did little to change the somewhat murky picture for TNX-355.

Still Deeper

Beyond the pipeline of drugs in human studies, there was interesting information on new drug targets. One such presentation was on APOBEC3G. APOBEC3G is a powerful anti-HIV enzyme that naturally occurs in human cells. Over the past few years, scientists have studyied this enzyme, trying both to understand how it works and, perhaps more importantly, how HIV overcomes it. Warner Green of the Gladstone Institute for Virology discussed research on this subject done by his group.

Again, APOBEC3G is a factor inside of cells that has anti-HIV activity. Researchers have found that an HIV gene product called Vif interferes with APOBEC3G in two ways. First, Vif binds to APOBEC3G resulting in the cell breaking the factor down and rendering it inactive against HIV. Second, Vif signals the cell to produce less APOBEC3G—a process called down-regulation. The combined effect is the almost total depletion of APOBEC3G from cells. Finding ways to interfere with the interaction between Vif and APOBEC3G is an attractive target for anti-HIV drug development. If you can keep Vif from attaching to the natural anti-HIV enzyme APOBECG3, it should be able to persist at high enough levels in the cell to block the virus.

Better using the tools we have

The conference also featured some noteworthy presentations on existing, approved anti-HIV drugs. Here are some highlights.

One interesting study compared a regimen with the GlaxoSmithKline protease inhibitor, Lexiva (fosamprenavir/ritonavir), to the "gold standard" regimen with Kaletra (lopinavir/ritonavir) from Abbott Labs. Regimens with Kaletra are one of only two first line anti-HIV regimens highly recommended by the Federal Guidelines. (The other is a regimen with Sustiva.) While there is little doubt that the Kaletra regimen is both highly potent and very durable, it has not been directly compared to a number of other regimens.

For a complete list of drug names and classes, see the DRUG ID CHART on page 10.

The study included 878 people taking either Kaletra or Lexiva, with Epzicom. (Epzicom is a tablet of Epivir + Ziagen [abacavir].) People who experienced an allergic reaction to Ziagen (about 6%) were allowed to switch to a different drug.

After 48 weeks, the percent of people who had undetectable HIV levels (under 50 copies) was virtually identical in the two groups, though a slightly higher percent of those taking Lexiva had viral loads below 400 copies. Average gain in CD4+ cell counts was also similar, with the Lexiva group gaining 176 cells and the Kaletra group gaining 191. Drug-related side effects were similar for both, as was the number of people who stopped therapy due to side effects.

The importance of this study for people just starting therapy is that Lexiva represents a third reasonable alternative to the highly recommended therapy options, giving people greater choice. However, it will take some time before this finding is reflected in the Federal Guidelines.

The overall significance of this study is somewhat moderated by another study that compared a similar Kaletra regimen to a Sustiva regimen. Researchers compared the two regimens most highly recommended in the Federal Guidelines (explained above), both taken with two NRTIs. The study also included a group taking only the two drugs, Kaletra + Sustiva, without any NRTIs.

The study followed 753 volunteers for an average of 112 weeks. At the end, there was no statistically significant difference in viral load among the three groups. However, there was a clear trend favoring Sustiva + two NRTIs and Sustiva + Kaletra as compared to Kaletra + two NRTIs. The Kaletra + NRTIs arm showed a shorter time to rebounds in HIV levels, which was a surprise to many. However, since the finding was not statistically significant, it is difficult to say just how important the observation is and whether it should affect treatment decisions.

Perhaps the most important finding of the study was that the group on Sustiva + Kaletra performed at least as well as the best conventional arm (Sustiva + two NRTIs). There is a growing interest among people with HIV, doctors and researchers in finding regimens that do not require people to take two NRTIs. Since 1996, nearly all regimens have included two NRTIs. Findings over the last several years have raised concerns over the toxicity of these drugs, and some researchers and activists believe people might fare better without them.

The combination of Sustiva + Kaletra points the way toward regimens that are highly potent and durable without using NRTIs. We believe this kind of research will eventually lead to widespread use of two-drug regimens and perhaps even one-drug regimens that work as well as today's three-drug combinations, but hopefully with fewer side effects.

Monotherapy: no longer a no-no?

Monotherapy (an anti-HIV drug regimen of one drug) was once among the most feared words in anti-HIV therapy. Now, it is making a bit of a comeback.

Spurred by a small study by Dr. Joe Gathe that showed surprisingly good results using the anti-HIV drug Kaletra alone, scientists have been re-examining the current three-or-more drug rule. Two presentations in Toronto highlight further research on this topic.

The 96-week MONARK study compares a relatively small group of people (136) taking Kaletra + Combivir (a pill of Epivir + Retrovir [AZT , zidovudine]) to people on Kaletra alone. Using a conservative analysis (called intent-to-treat) after 48 weeks of follow-up, 71% of people taking Kaletra monotherapy had viral load below 50 copies, compared to 75% of those on Kaletra + Combivir.

A much bigger difference was seen when just looking at people still in the study at 48 weeks (called as-treated). Looked at this way, 84% of people on Kaletra alone had viral loads below 50 copies, while 98% of people on the Kaletra + Combivir combination had HIV levels below 50. This suggests that when people are able to tolerate three-drug combinations, they may be more likely to achieve undetectable viral loads with the current three-drug approach than this experimental one-drug approach. However, for those who can't tolerate and/or aren't able to access three drugs, Kaletra monotherapy might offer an alternative.

There are two ways to interpret these results. One way is to look at the somewhat better results for people taking the traditional three-drug combination, and conclude that this tried-and-true method is superior. Another way is to see that by either analysis, most people taking Kaletra alone were able to achieve and maintain undetectable viral loads.

The lead investigator of this study claimed that everyone taking Kaletra alone who started the study with less than 100,000 copies of virus achieved viral load under 50 copies at 48 weeks. This suggests that a person's initial viral load before starting treatment may be an important factor in determining whether it is safe to use monotherapy. However, this needs to be confirmed in larger and longer studies.

In another study, people with undetectable viral loads taking a three-drug combination of Kaletra + two NRTIs were randomized either to stick with their three-drug combination or switch to a maintenance regimen of Kaletra alone. This approach to therapy is frequently called an "induction/maintenance strategy" or a detensification strategy. After 48 weeks, 85% of people taking Kaletra alone maintained viral loads below 50 compared to 90% of people taking Kaletra + two NRTIs. The difference was not considered statistically significant.

There are four important reasons to continue looking at reducing the number of drugs people with HIV must take. The first is long-term side effects. Hopefully by reducing the number of drugs people take, the less long-term, accumulated toxicity will result. Second, fewer drugs in a regimen could lead to more regimens available to people over the course of their lives. Third, fewer pills are simply easier to take. Fourth, taking fewer drugs can greatly reduce the cost of therapy. In the international setting, this reduced cost could result in a much greater number of people being treated.

While these monotherapy reports look encouraging, people should not rush to stop combination therapy or de-intensify their regimens. Lessons learned from other research on simplifying regimens showed us that short-term success fell apart over the long-term and many who acted on early data risked developing resistance. This is definitely important research to follow, but it's likely too soon to start making changes in therapy based on these results.

drug i.d. chart

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

The results of these two studies are encouraging and argue for more research on simpler anti-HIV drug regimens. Earlier in 2006, preliminary findings were presented on monotherapy using another boosted protease inhibitor, Reyataz (atazanavir). For a drug to be a good candidate for monotherapy it must be potent and be difficult for HIV to develop resistance to. Such drugs are said to have a high genetic barrier to resistance, which means HIV must acquire a number of mutations before it shows resistance to a drug. Currently, only boosted PIs meet these criteria (like Kaletra), but novel drug targets, like integrase inhibitors, might offer more potential for this approach down the line.

Final thoughts

The 2006 International AIDS Conference in Toronto is unlikely to be remembered for any major scientific breakthroughs or advances. The enormity of the pandemic was evidenced by both the number of delegates—over 30,000—and the scope of work they represented. As we begin to look past the 25-year anniversary of the pandemic, there is much to be hopeful for. New drugs and new ways of using old drugs are on the way. Basic science on HIV drugs and HIV disease, continues to expand our understanding of the disease, moving us closer each day to our ultimate goal—a cure for HIV/AIDS.

Pipeline Update: Short Notes on New Anti-HIV Drugs in Development

Project Inform follows HIV drug development closely, in order to provide people living with HIV accurate and up-to-date information on new drugs as they work their way through the development process. HIV treatment activists use the term pipeline to refer to the collection of all experimental HIV drugs. This article provides a very brief overview of each of the most promising drugs now in the pipeline. See the box on page 12 for more information on the phases of clinical studies.

Integrase Inhibitors

MK-0518 is the first of an entirely new class of drug, called integrase inhibitors, being developed by Merck. It is currently in Phase III studies. Encouraging data on MK-0518 in people who have used anti-HIV therapy (called treatment experienced people) were presented at the 2006 Conference on Retroviruses and Opportunistic Infections (CROI). This study showed the drug to be remarkably effective in reducing viral load in people who were highly resistant to nearly all other anti-HIV drugs.

More data, this time in people taking anti-HIV medications for the first time, were presented at the 2006 International AIDS Conference (IAC, visit *www.projectinform.org/blog_01_md.html*). Still more was presented at Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in September 2006. Some of the more striking data shows that the drug appears to reduce viral load more quickly than other potent anti-HIV drugs.

Yet another promising observation, from a study that compared a regimen based on MK-0518 to one based on the popular drug efavirenz, concluded that people treated with MK-0518 showed lower levels in serum cholesterol and triglycerides, while efavirenz like most other NNRTIs and protease inhibitors (PIs), increased both. This is considered a welcome change since many people who take anti-HIV drugs experience problems of increased cholesterol.

While there is still much to learn about MK-0518, so far it looks exceptionally potent and well tolerated. The drug is taken as a single pill twice a day and, unlike most PIs, it does not require using Norvir (ritonavir) as a booster. Merck recently announced the opening of their expanded access program (visit *www.projectinform.org/blog_02_md.html*). We expect data to be submitted to the Food and Drug Administration (FDA) for consideration for approval in 2007.

GS-9137 is a competing integrase inhibitor being developed by Gilead Sciences. It is currently in Phase II studies. Data were presented earlier this year from a Phase I study in HIV-negative people. A Phase II study in HIV-positive people, comparing GS-9137 to Norvir-boosted PIs, is fully enrolled. This drug is taken once daily but requires Norvir as a booster.

The integrase inhibitor currently known as 364735 is being developed by GlaxoSmithKline and Shionogi. The completion of its Phase I studies was announced at the 2006 IAC. Data are expected sometime in 2007.

The Phases of Drug Development

- Phase I studies are small and are designed to get information about a new drug's safety and how people respond to different doses. These studies are generally the first time a new drug is given to people, so they include a small number of people (around 10–30), are short in duration (around 1–8 weeks), and often will test a variety of doses.
- Phase II studies involve more people (around 30–200 people) and last somewhat longer (12–48 weeks). Sometimes Phase II studies examine different doses of a drug and look for specific drug-drug interactions. In HIV, these studies will often reveal early information about whether a drug is active against HIV.
- Expanded Access Programs (sometimes called parallel track) are programs that provide early access to drugs that show promise in Phase II studies. They also help build a database about a drug's side effects, and therefore its safety. While there aren't hard and fast rules, these programs will often open at the end of Phase II studies or during Phase III studies once the Phase III study is fully recruited. In HIV, they have typically been designed to provide access to new drugs to people who have few options and who don't qualify for other ongoing studies.
- Phase III studies are larger (several hundred to a thousand or more people) and last longer (minimally 24 weeks to several years). In addition to looking at drug safety and side effects, Phase III studies look for conclusive evidence of a drug's effectiveness. These are usually the pivotal studies that determine whether a drug is approved.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Etravirine (TMC-125) is being developed by Tibotec Therapeutics and is currently in Phase III studies. Data thus far suggest it is effective against HIV that is resistant to the available NNRTIs, like Sustiva (efavirenz) and Viramune (nevirapine). In addition to its stand-alone Phase III program, etravirine is being studied together with the recently approved PI Prezista (darunavir, TMC-114), in a landmark study called DUET. While this drug is designed to overcome resistance to other NNRTIs, research has shown that HIV that develops resistance to etravirine is also resistant to Tibotec's other experimental NNRTI, rilpivarine (TMC-278). Thus, if people use etravirine now and eventually develop resistance, rilpivarine will unlikely be an option for them in the future. An expanded access program for etravirine opened recently and the details are posted on Project Inform's website at *www.projectinform.org/bn/bnews_091106.html*.

Tibotec Therapeutics' rilpivarine (TMC-278) is currently in Phase II studies. Data were presented at the 2006 CROI showing adequate levels of drug in the blood (called pharmacokinetics) and that HIV had difficulty developing resistance to the drug. Like Tibotec's etravirine, rilpivarine is designed to overcome resistance to the approved NNRTIs. Little is known about the strength or side effects of rilpivarine yet. A Phase II study in treatment experienced people has fully enrolled, and data are expected in 2007.

BILR-355 is being developed by Boehringer Ingelheim and is currently in Phase I/II studies. Early data suggest it will work against HIV that is resistant to the approved NNRTIs. A Phase II study in people on a failing anti-HIV drug regimen is ongoing. BILR-355 must be taken with a booster dose of Norvir. No information is yet available on whether BILR-355 is cross-resistant with etravirine and rilpivarine.

Nucleoside reverse transcriptase inhibitors (NRTIs)

Racivir is being developed by Pharmasset and is currently in Phase II studies. This drug is very similar to Epivir (lamivudine, 3TC) and Emtriva (emtricitabine, FTC). Racivir is active against the hepatitis B virus as well as HIV. Early research suggests that it takes longer for HIV to develop resistance to racivir than to either Epivir or Emtriva. If more research confirms this, it might make racivir an attractive alternative to those drugs for first line therapy. There is an ongoing Phase II study evaluating racivir in people with Epivir-resistant HIV.

Elvucitabine is being developed by Achillion and is currently in phase II studies. In 2005, early information suggested that this might be the first anti-HIV drug taken once a week, although currently it is being studied as once a day. At the higher doses (50mg and 100mg weekly) being studied once a week, the drug proved too toxic, dangerously suppressing the development of new cells in the bone marrow (called bone marrow toxicity). This hampered drug development and the company is now studying it at lower doses (5mg and 10mg) daily, where hopefully this side effect won't be a problem.

Apricitabine (AVX754) is being developed by Avexa Pharmaceuticals and is currently in two ongoing Phase II studies. One is an extension of an earlier study and is looking at safety and tolerability of long-term use in people who had completed the earlier study. The second is examining

several doses of apricitabine in people whose HIV shows evidence of the M184V mutation, which is associated with resistance to the NRTIs Epivir and Emtriva. Earlier research showed people who took different doses of apricitabine averaged between 1 and 1.6 log reductions in HIV levels, which is similar to the levels of viral suppression seen with drugs like Epivir.

Entry Inhibitors

Maraviroc (UK-427-887) is a type of entry inhibitor called a CCR5 inhibitor. It is being developed by Pfizer Pharmaceuticals and is currently in Phase III studies. Maraviroc is expected to be the first-in-class CCR5 drug when it is approved. Results from studies so far have shown that it works well both in people new to HIV treatment and treatment experienced people.

One of the concerns with all drugs that interfere with CCR5 is that using them may force HIV to begin using another entry point called CXCR4. HIV that uses CXCR4 has been associated with more rapid disease progression. Data from studies thus far have suggested that this feared switch is happening only rarely and that it hasn't been associated with more rapid disease progression.

One of the open questions about maraviroc and other co-receptor (CCR5 and CXCR4) inhibitor drugs is whether and how to use lab tests to determine who could best benefit from them. This blood test is called a tropism assay. A presentation at the 2006 IAC suggested that maraviroc could be used safely in people with HIV that uses both receptors—called dual tropic virus.

An expanded access for maraviroc is being developed. Details on this program will be posted on Project Inform's website (www.projectinform.org) when they are known.

Vicriviroc (Schering-D) is another CCR5 inhibitor. It is being developed by Schering-Plough and is currently in Phase II studies. Research has been slowed by underwhelming results and concerns about the rate of cancers seen in people taking the drug. In late 2005 a study comparing vicriviroc (together with approved anti-HIV drugs) to Sustiva (also together with approved anti-HIV drugs) was halted because significantly more people taking vicriviroc experienced rises in viral load, compared to those on Sustiva. More recently, a presentation at the 2006 IAC showed good reductions in viral load for people taking vicriviroc. However, of concern was the higher rate of cancers seen in the people taking the drug. The rates were not considered high enough for the study to be halted.

There are several ongoing studies of vicriviroc. A Phase II study is looking at two doses (20mg and 30mg once a day) of vicriviroc together with more traditional anti-HIV therapies (often called optimized background anti-HIV therapy as in these studies researchers work with volunteers to devise potent regimens with the existing drugs) in people with resistance to other HIV drugs. Another planned study, that is not yet enrolling volunteers, is a Phase III study which will look at vicriviroc in people with dual tropic HIV.

TNX-355 is a type of entry inhibitor called an attachment inhibitor. It is being developed by Tanox Pharmaceuticals and is currently in Phase II studies. It is a kind of immune system protein, called a monoclonal antibody (mAb). This particular artificial antibody aims to stop HIV from attaching to the CD4+ receptor that it uses to enter cells. It is given through a needle placed in a vein in the arm, every two weeks. This route of delivery—called intravenous (IV) infusion—likely will restrict its use to people with extensive treatment experience and a lack of other treatment options.

Data presented thus far on TNX-355 have been somewhat confusing. In addition to only modest reductions in HIV levels, there was a lack of a dose dependant response. Typically the more of a drug that is given to a person, the larger the anti-HIV reductions they experience. This hasn't been the case with TNX-355. While the full implications of this finding aren't yet understood, it raises questions for activists and researchers alike. A final concern about TNX-355 is what it is likely to cost if approved, which is expected to be quite high.

Such concerns, however, should not prevent researchers and companies from studying drugs like this. We do not yet know where the next real advance might come from or what pathways of research will eventually lead to a cure. Some approaches, such as drugs that require IV infusion or might be unduly expensive, may still have an important role to play in the overall progress of AIDS research.

New production methods can perhaps overcome pricing issues, while newer formulations may result in less frequent dosing. For example, the current version of Fuzeon (enfuvirtide, T20) requires two daily injections. This has been an obstacle for many people. But things that were learned while developing the original drug have now led to the testing of a second generation product that may require dosing only once a week.

Conceptually, dosing once a month may someday become possible. Thus, we must be careful not to reject new approaches simply because their first generation products are less than ideal. First generation protease inhibitors weren't so good either, but the current generation is proving to be far superior.

PRO-140 is another monoclonal antibody, but this one is more like maraviroc and vicriviroc in that it is a CCR5 inhibitor. PRO 140, from Progenics Pharmaceuticals, is currently in Phase IB. Like TNX-355, it is given through IV infusion. The exact dosing and dosing schedule have yet to be determined.

Data presented earlier this year show that at the highest dose given to volunteers (5mg/Kg), PRO-140 remained attached to cells 60 days after infusion. It is not yet clear what this means about how often the drug will need to be given to patients, but surely it won't require daily dosing. Ongoing studies will help choose an optimum dose and schedule for infusion. Because it is given through an IV, it is likely to be restricted to people with extensive treatment experience. There is also concern about its cost if it is approved, as other drugs of this type are quite expensive.

Protease Inhibitors

PPL-100 is being developed by Ambrilia Biopharma and is just entering Phase I studies. Data from test tube and animal studies suggest it might work against HIV that is resistant to other PIs.

Brecanavir (GW640385) is being developed by GlaxoSmithKline and is currently in Phase II studies. Brecanavir must be taken with a booster dose of Norvir. Early data have been encouraging. Results from a 48-week, 31-person open label study (where participants knew they were taking the drug) of brecanavir plus two NRTIs were presented in 2005. After 24 weeks most people had viral loads below 50 copies. Average reductions in viral load ranged from over 3 logs in people taking HIV drugs for the first time, to just over 2 logs in people with protease resistant HIV. Phase II studies are ongoing now.

Other Types of Anti-HIV Drugs

KP-1461 is a new type of anti-HIV drug, called a mutagenic nucleoside competitor reverse transcriptase inhibitor. It is being developed by Koronis Pharmaceuticals and is currently in Phase I studies. Unlike other anti-HIV drugs that seek to limit HIV's ability to mutate, KP-1461 works by accelerating its mutations. The ultimate goal is to force HIV to gather so many mutations that it is no longer able to replicate—something called terminal mutagenesis. This drug is just entering human studies, so little is known to date. This drug's unique mechanism raises difficult questions about how it will be studied and evaluated. It's definitely research to watch.

Bevirimat is a maturation inhibitor (MI) being developed by Panacos Pharmaceuticals. It is currently in Phase II study. Maturation inhibitors work near the same point in HIV's replication cycle as PIs. While PIs work by physically blocking the protease enzyme, MIs like bevirimat, work by attaching to immature HIV proteins and preventing the protease from cutting them up. Data from a Phase II study showed that people taking 200mgs of bevirimat once a day averaged about a 1 log reduction in HIV levels. A Phase II study in treatment experienced people is enrolling now.

Salvage Challenges

2006 and 2007 may one day be remembered as true watershed years for people with advanced HIV disease. The approval of Prezista (darunavir) in spring 2006 and the introduction of the integrase inhibitor MK-0518 through expanded access have brightened the picture for people who have already used many anti-HIV therapies and classes of therapy and need new options.

Simply put, a great majority of people who might have given up hope of achieving "undetectable" viral load can now do so. Less certain, but also holding hope for treatment veterans, are the entry inhibitor maraviroc and the NNRTI etravirine. Etravirine is now available through expanded access for people who have failed other drugs in this class (Viramune [nevirapine], Rescriptor [delavirdine] and Sustiva [efavirenz]), while the announcement of a similar program for maraviroc is expected before the end of the year. While celebrating the very real victories that these drugs represent for people with HIV, a look deeper into the anti-HIV drug development pipeline raises new and difficult questions about the future of drug development for treatment experienced people.

Treatment Experienced: The faster fast track

For several years now, most companies seeking fast approval of new anti-HIV drugs have focused on people with extensive treatment experience—a group sometimes called treatment experienced or more problematically salvage patients. Scientific, medical and financial factors made this strategy attractive for companies moving their experimental anti-HIV drugs through the Food and Drug Administration (FDA) approval process.

Companies would design studies around patients who were failing existing therapies and add either the new drug or a placebo to the regimens. If the added drug did more than a placebo, it was seen as proof of the drug's effectiveness. Could impressive results now from the two latest drugs

change this model and force companies to find new ways to study their drugs? Whatever the answer, this new landscape raises important questions for companies, the FDA and activists about the future of drug development for treatment experienced people.

There was a time when activists fought tooth-and-nail with pharmaceutical companies to include treatment experienced people in their studies. Historically, companies had been hesitant to study their new drugs in this population, fearing the results would harm their drugs' chance at being approved by the FDA. This fear was not unfounded. People with more advanced HIV disease, especially those with extensive drug experience, tend to get less of a robust response to anti-HIV drugs than those earlier in disease or newer to treatment. Moreover, they tended to suffer more serious side effects because of their weakened condition. Still, they were the people who needed new and better drugs the most. Project Inform, along with other treatment activists, consistently raised the demand that new drugs be studied in these people.

It is a battle that activists and treatment experienced people largely won. The companies were made to see that scientifically, ethically and even financially it was to their advantage to study new drugs in treatment experienced people. In fact, the pendulum swung fairly far in this direction, where most recently approved HIV drugs were studied first in treatment experienced people. In some cases, like Aptivus (tipranavir) and Fuzeon (enfuvirtide, T20), the drugs are still used almost exclusively by treatment experienced people. In other cases, most notably Viread (tenofovir), the drugs are now used widely as part of first and second line therapy, even though it was first tested in salvage patients.

Two important economic factors drove this change. The first was the amount of time it takes to move a new drug through the FDA approval process. By studying a drug in treatment experienced people, this amount of time is shortened significantly. It takes less time to see if a therapy is working or adding something when given to people with few options and a high likelihood of HIV disease progression. The shortened time to approval has a significant impact on the amount of money a company needs to invest in a new drug. The faster it is approved, the less money the company spends. It also allows the company to begin recouping those costs by selling their drug earlier.

The second factor was the effectiveness of existing drugs for first line therapy. Drugs like Kaletra (lopinavir/ritonavir) and Sustiva—combined with a backbone of two NRTIs—were achieving very good results both in studies and in everyday medical practice. The perception developed that the market for first line therapy was crowded and offered little space for a new entrant and, indeed, little room for improvement.

It made sense scientifically and medically to study a new drug in treatment experienced people. This too stems from that same effectiveness of the first line drugs. To gain approval for first line therapy, a new drug would need to have similar, if not superior results to drugs, like Kaletra and Sustiva, already being given as part of first line therapy.

Aptivus: The eye of the beholder

In terms of both potency and tolerance, the standards of success, for use in treatment experienced people are different than for first or second line therapy. The protease inhibitor Aptivus provides a good example of this. Its mediocre potency and troubling, sometimes dangerous side effects make it a poor choice for people with other options available to them. For people who have few options,

the risks of liver problems, cerebral hemorrhage and the required high dose of Norvir (ritonavir) to boost it might be more acceptable. This is an example of the need to look at cost-benefit equations in context. Side effects and inconvenience that might be intolerable to a person with many choices, often looks very different to a person with fewer choices. (For more information about Aptivus, read the publication, *Aptivus*, available at *www.projectinform.org/fs/tipranavir.html*.)

This favorable landscape for studying new HIV drugs in treatment experienced people has led to the approval of some important new drugs and no doubt has saved lives. This landscape however is not fixed or static. It is based on an evolving set of variables, most importantly the strength and tolerability of the drugs already available. Two new drugs, the recently approved protease inhibitor Prezista (darunavir) and the experimental integrase inhibitor MK-0518 seem likely to bring significant changes to this equation.

Prezista: Real hope for the really experienced

Prezista was approved in Spring 2006 based on two large studies (POWER 1 and POWER 2), which compared it to other Norvir-boosted protease inhibitors in treatment experience people. The results from these studies were very promising; with more than three times as many people taking Prezista having a sustained reduction in viral load compared to those taking other boosted protease inhibitors. Prezista offered a real advantage for people who had developed resistance to most other protease inhibitors.

The results achieved with Prezista were, at the time, unprecedented. The volunteers in the two studies were highly treatment experienced, having taken drugs from the three major classes (PIs, NNRTIs and NRTIs), and having an average of three major PI-associated resistance mutations. By comparison, in a similar study of Aptivus for treatment experienced people, about half as many people had viral loads below 50 copies after 24 weeks (23% for Aptivus vs. 46% for Prezista). (For more information about Prezista, read the publication, *Prezista*, available at *www.projectinform.org/fs/prezista.html*).

MK-0518: A new approach sets new standards?

Early results of studies of another new drug, called MK-0518, are equally good and possibly better. MK-0518 is one of a totally new kind of HIV drug called an integrase inhibitor, and as such, should be fully effective despite any and all resistance to previous drugs. Integrase inhibitors are drugs that stop HIV from combining its genetic material into a cell's own genes. There are several of these drugs in development, with MK-0518 the furthest along.

At the 2006 Conference on Retroviruses and Opportunistic Infections (CROI), researchers presented data on MK-0518 showing large decreases in viral load when the drug was given to treatment experienced people. In one study of treatment experienced people, 72% of people taking MK-0518 had viral loads below 50 after 16 weeks, compared to 16% of people taking a placebo. (Both groups took at least two other approved anti-HIV drugs.) The data raised the possibility that MK-0518 might well be the most potent drug to date for treatment experienced people.

Equally impressive and possibly more interesting was the rate at which people experienced drops in their viral loads. In a study presented at the 2006 International AIDS Conference (IAC),

researchers presented data from another phase II trial, comparing MK-0518 to Sustiva [both plus Epivir (lamivudine) and Viread (tenofovir)] in people taking HIV drugs for the first time. While similar numbers of both groups ultimately achieved viral loads below 50 copies after 24 weeks, on average people taking MK-0518 achieved undetectable viral load more quickly. While more research is needed to fully understand this finding, most previous research has shown that the faster HIV viral load drops, the longer lasting the effect.

Yet another study, presented at ICAAC in San Francisco in September 2006, compared MK-0518 to Sustiva in an otherwise identical regimen and measured the effect of the two regimens on cholesterol levels. *Hyperlipidemia*, or abnormally high cholesterol levels, has been a common effect of most protease inhibitor regimens as well as regimens based on Sustiva. Hyperlipidemia is associated with many harmful side effects. After 24 weeks, the patients treated with MK-0518 actually showed a statistically significant reduction in cholesterol levels compared to those on Sustiva, who experienced the usual increase.

(Phase III studies are currently underway for MK-0518. On the final day of the 2006 IAC, Merck announced the opening of an expanded access program for MK-0518. For information on this program, visit *www.projectinform.org/bn/bnews_090806.html.*)

The results from Prezista and MK-0518 make it clear that the bar has been raised for developing new drugs in treatment experienced people. The results from these two drugs make it clear that the picture for treatment experienced people looks better than ever. However, it is almost certain to substantially reduce the number of people failing all therapies. This is good for those people, but it will also greatly reduce the number of people in need of salvage studies and drugs for this use. The number of people in need of salvage therapy has been decreasing slowly for a number of years. These two new highly potent drugs seem likely to accelerate the decline. Again, good for the patients, not so good for companies trying to get drugs approved for salvage use.

A look at two drugs being studied in treatment experienced people shows the potential dilemma for the companies that are developing them, for the activist community and for the FDA.

TNX-355: Fuzeon Redux?

TNX-355 is a kind of entry inhibitor, called a monoclonal antibody (mAb). TNX-355 is a protein that binds to another protein on the surface of immune system cells, called CD4+. HIV attaches to the CD4+ protein in order to enter an immune cell. TNX-355 attaches to the CD4+ protein in such a way that HIV can't.

TNX-355 is given by intravenous infusion every two weeks, likely restricting its use to treating experienced people. Tanox, the company developing TNX-355, is studying their drug exclusively in treatment experienced people. Unfortunately, the results seen so far do not compare favorably to Prezista or MK-0518. Studies of TNX-355 in treatment experienced people showed a maximum viral load reduction of around 1 log—compared to almost 2 logs (10 times more) for MK-0518.

Bevirimat: Is being first enough?

Bevirimat (PA-457), the first maturation inhibitor to be studied in people, faces some similar obstacles. Maturation inhibitors work at a similar place in the HIV replication cycle as protease

inhibitors. While protease inhibitors work by attaching to the protease enzyme and blocking its activity, bevirimat works by attaching to the proteins that the enzyme cuts up (substrates) keeping them from being cut up by the protease enzyme.

Unlike TNX-355, bevirimat is a small molecule, so it can be given as a pill. Like TNX-355, results from early studies have shown moderate anti-HIV activity. In studies published so far, people taking bevirimat sustained about a 1 log reduction in viral load. This is similar to TNX-355, but less than what was seen with either Prezista or MK-0518. While larger studies continue, and necessary to fully understand the strength and other characteristics of bevirimat, these early results raise the question of what role this drug will have for treatment experience people.

The more important issue here is not the merits of bevirimat or TNX-355 but with the changing realities facing companies that seek to develop new HIV drugs, the FDA that decides on approval, and the activists who follow and influence the process. The simple, fast route for developing these drugs is going away and won't come back for quite some time. Many companies have shied away from developing new drugs for first line therapy, knowing they would have to study their new drug against the proven first line drugs Kaletra or Sustiva. A similar situation might now be developing for companies seeking to develop their drugs for treatment experienced people.

It remains to be seen how different companies, the activists or the FDA will respond to these changes. While it isn't hard to see that the landscape has changed, how exactly to respond to these changes is far less clear. For the companies, an honest evaluation of the potential for their drugs in this current climate is crucial. For the FDA a similar discussion of the standards to evaluate these new drugs is necessary. So too must the activists (Project Inform included) reevaluate and adjust our approaches to activism for treatment experienced people. This is not to suggest that drugs like these shouldn't be studied or developed, but only that new approaches to their development must be created.

The very real challenges of anti-HIV drug therapy for treatment experienced people remain. While the advances represented by Prezista and MK-0518 are welcome, far too little is known about these drugs. It will take more research, as well as the real world experience of people with HIV using these drugs to fully flesh out their strengths and weaknesses. Despite the development of these two new drugs, there will still be a need for new anti-HIV drugs, especially for treatment experienced people. It is undeniable that companies seeking to develop these new drugs face higher expectations than ever before. For people with HIV and the activist community, this is a good problem to have. Project Inform remains committed to facilitating the study and development of new drugs, especially for those who need them the most.