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

P.I. Perspective

October 2007, Issue #44

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

An historic turning point arrives for HIV therapy

The Conference on Retroviruses and Opportunistic Infections (CROI) in the US and the International AIDS Society (IAS) conference elsewhere are two of the most important annual HIV science gatherings each year. This year's meetings, held in Los Angeles and Sydney Australia, included literally thousands of posters and presentations, on topics spanning the HIV science spectrum, from antiretrovirals to opportunistic infections and microbicides. This issue of *PI Perspective* will cover some of the most important stories from this year's meetings, from new anti-HIV drugs, new research on older anti-HIV drugs as well as areas like cardiovascular disease and lipodystrophy.

The big story

The International AIDS Conference in Vancouver in 1996 ushered in the era of Highly Active Anti-Retroviral Therapy (HAART). Data presented there from several groups introduced a new paradigm in the treatment of HIV disease, where long-term suppression of HIV replication was possible and the concept of "undetectable" viral became the new goal of treatment. Dramatic drops in death and serious illness associated with HIV/AIDS were seen throughout the late 1990s. Despite the obvious benefits, however, drug side effects and the development of resistance made it clear that still better drugs were needed.

As we rightly celebrated each advance in HIV care and treatment there was one group for whom the picture wasn't as bright. Sometimes called *salvage patients*, these were people with extensive resistance to available anti-HIV drugs. This sometimes included people who had begun with AZT monotherapy in the late 1980s, and had cycled through round after round of helpful, but not fully suppressive drug therapy. One of the challenges they faced was the inherent conflict between the requirements of the new treatment paradigm and the erratic and difficult-to-predict drug development process. Success with treatment was believed to require that a patient take three active drugs at the same time. But with their health and lives in the balance, people had to take each new drug as it became available, often without enough other fully active drugs to support the new drug—a situation called *serial monotherapy*.

When the protease inhibitor Prezista (darunavir) was approved toward the end of 2006, following upon the approval of Fuzeon a few years before, the possibility for something better began to emerge. The introduction of this new drug was important in two ways.

CONTENTS

1–4 An Historic Turning Arrives Point for HIV Therapy
4–8 Shape-Shifting: The Art of Drug Pricing
8–19 Update on Experimental Antiretrovirals
19–23 Flu Shots and the Next Flu Season
23 Reyataz Monotherapy Study Stopped
24 Dutch Study Finds Treatment Interruptions Safe for Some

First, studies showed it was one of the most effective drugs to date in treatment experienced people, with over 60% of people taking it able to achieve undetectable viral loads. Second, it was approved just as three other new drugs were far along enough in their development that they were becoming available through expanded access programs. This meant that rather than the dead-end of serial monotherapy, people might be able to construct truly viable regimens with two or three new, active drugs.

Expanded access times three

With this in mind, Project Inform, along with other advocates, argued successfully for the companies with expanded access drugs to allow other experimental agents to be used alongside theirs, when safety and drug interaction concerns were adequately understood. Typically when a drug is offered to people in expanded access programs, they are only allowed to use it with already approved drugs. This agreement, by all three companies (Pfizer, Merck, and Tibotec), to permit the use of other experimental drugs in their expanded access programs is a good example of treatment advocacy in action. It also offers a hint of the good that might be done when pharmaceutical companies cooperate and not just compete.

It isn't just the number of new drugs, but the qualities of the drugs themselves. Two are entirely new types of drugs, from new classes. This is crucial for treatment experienced people, who may harbor a large degree of resistance to the older classes of anti-HIV drugs. They are the *CCR5 antagonist*, Selzentry (maraviroc) and the *integrase inhibitor* Isentress (raltegravir). The third drug is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) called etravirine. Unlike the other NNRTIs, which have a high degree of cross-resistance, etravirine works against HIV that has developed resistance to other drugs from this class, like Sustiva (efavirenz) and Viramune (nevirapine).

Following up on the success of Prezista, the data presented at the CROI and IAS conferences on both Selzentry and Isentress show that achieving an undetectable viral load is now possible for many people who may have never been able to. In one study of Isentress, over 90% of people taking along with two other active drugs had undetectable viral loads after 6 months. While the numbers for Selzentry weren't quite as striking, they were impressive nonetheless—with around 2 out of 3 people achieving viral loads below 400 copies.

Little data on the third new drug, etravirine, were available at the time of the CROI meeting, but results presented at the more recent IAS meeting showed convincing evidence that it works well in most people who have developed resistance to the older NNRTIs. The pivotal studies that will be used to secure FDA approval, called Duet 1 and Duet 2, showed that etravirine works best against HIV that has fewer NNRTI associated mutations. If one or fewer NNRTI mutations were detected at baseline, 60–75% of people taking etravirine achieved HIV levels below 50 copies. When three NNRTI mutations were present, that number dropped to 45%; with 4 only 25% reached the goal. When five NNRTI mutations were detected, only 15% of people achieved HIV levels below 50 copies. Still these are promising results for people who can no longer take NNRTIs due to resistance and the drug clearly fills an unmet and important need. When its success is considered alongside the results shown by Prezista, Selzentry and Isentress, it's clear that this an entirely new era in the treatment of HIV.

Introducing the session at CROI where some of these results were first presented, Dr. John Mellors remarked that he didn't think it was an exaggeration to say that this marked an important milestone for the treatment of drug-resistant HIV. Project Inform shares that view—the stars have indeed aligned and people with HIV, perhaps as never before, and most importantly even heavily treat-

In memory of ...

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

Richard Cazen, MD

Rolph Shanabruch

Eugene Gardner

ment experienced and drug-resistant have reason for a renewed sense of hope. All of these drugs are being studied mostly in treatment experienced people. When they are approved, it will likely be restricted to people with significant experience with other HIV drugs. It is difficult not to speculate, though, on how these drugs will also affect the treatment of people just beginning therapy. At the very least, people will soon have many new and improved options that will almost certainly lead to new paradigms at every stage of HIV treatment.

Both Isentress and Selzentry are already being further studied in less treatment experienced people. In fact, intriguing early results from one study (presented last year) of Isentress in people taking HIV drugs for the first time suggested that it might have unrivaled potency as first line therapy. A longer term follow-up of this study presented at IAS showed long-term success and continued powerful suppression of HIV. We will follow this research closely. Data were presented in Sydney comparing Prezista to the gold standard Kaletra in people taking HIV drugs for the first time. This study was the first head-to-head comparison where any drug was able to prove superiority to Kaletra. In contrast, however, results from a study comparing Selzentry to Sustiva as first line therapy, showed that Selzentry didn't quite match up.

A note or two of caution is warranted. The data seen thus far on these drugs is very encouraging, but much more is needed. In each case, only several hundred people have taken the drugs and not for very long. The drugs appear to be potent and safe. Only long-term study, along with clinical use will allow us to fully understand the strengths and weaknesses of each of these new treatments.

Of particular importance is the concern around resistance, especially with Isentress and Selzentry, as they are from new classes. While research to understand resistance to these new drugs has been done, it is fair to say that this is the question that is the least understood at the moment.

While lab tests can help us know what to look for around drug resistance, clinical trials and real world use is needed to fully understand how prone to resistance these drugs are. There are two main factors involved in HIV drug resistance. The first is how much HIV needs to change, or mutate, to evade a drug. This is sometimes referred to as the *genetic barrier* to resistance—the more mutations that need to develop, the higher the genetic barrier. The second factor is a drug's potency—how well it reduces viral replication. Simply put, the less HIV replicates, the fewer opportunities it has to develop mutations and grow resistant to the drugs.

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

Too often, HIV drug resistance is talked about only in terms of the genetic barrier. While the genetic barrier is a vital factor, it fails to tell the whole story. The drug Sustiva (efavirenz)—widely used in first line therapy—offers a good example. HIV can develop resistance to Sustiva with a single change in its genetic code (called a *point mutation*). So, it has a very low genetic barrier to resistance. However, it is also quite potent—meaning it is able to reduce HIV levels very well. If you just looked at the genetic barrier, you might predict that resistance to Sustiva would develop quite rapidly. When you also factor in its potency, it is easier to understand how so many people have stayed on it for so long.

Of course, there is a third important factor in the durability of any drug regimen: adherence. Resistance to any HIV drug is less likely to develop the more consistently people can take it. Accurately predicting adherence is tricky, as many factors influence the ability of people to stick to their regimens. Two crucial drug-specific (in contrast to personal issues like depression) factors that influence adherence are ease of use, and tolerability. All of these new drugs are taken twice a day, and have good safety and tolerability profiles so far.

Final thoughts

With all of this in mind, there is little doubt that this is a truly rare moment. People with highly drug-resistant HIV have a number of powerful, well tolerated new drugs to build effective regimens around. In the third decade of this pandemic, this is the fist time we have had this many new drugs available at the same time. It may very well be the only time we do.

The goal of undetectability has been out of reach for too many people for too long. In talking with people around the country, we have been hearing from heavily treatment experienced people able to achieve undetectable viral loads for the first time ever. While these hopeful stories need to be backed up by controlled scientific studies and real world, they are hopeful nonetheless.

If you are a person with drug resistant HIV, it's crucial to make the most of this opportunity. This doesn't necessarily mean that you should start taking one, two, three or all four of these new drugs. It does mean working closely with your health care team, including an experienced HIV medical provider, to evaluate the options available to you and build a drug regimen that is the most likely to work for you. The goal of therapy for everyone now should be to reduce viral levels to undetectable, whenever possible. That goal is more possible for more people than ever before.

Shape-Shifting: The Art of Drug Pricing

On the day the announcement went out that the Food and Drug Administration had approved the new oral entry inhibitor Selzentry (maraviroc), the price was announced at $29 per day or $10,585 per year. Whether this sounded like a lot or about average depended in what country you live and what you know about drug pricing. Without knowing what other drugs cost, it would be difficult to understand what it meant at all. The purpose of this article is to share some of the background on drug pricing and community efforts to put a lid on the price of new drugs.

Early demonstrations expose high pricing

In the early days of AIDS activism, drug pricing was handled on a largely reactionary basis. We waited until a company announced a price, then we all screamed in unison that it was way too high. In a few cases, community groups were able to mount demonstrations and actions that led to a reduction in price over time, but there were in fact very few examples of this actually working.

The best known case was the fight against the original price of AZT, which led to demonstrations and even protests on the New York Stock Exchange and at the offices of the manufacturer. The price of AZT was eventually reduced, though a large portion of the actual reduction was due to a reduction in the dosage of the drug used, dropping from the original recommendation of 1,200mg per day down to the 600mg per day used currently in most settings.

Still, the demonstrations were successful because drug prices rarely go down. In later years a similar reduction was achieved in the price of acyclovir—a drug used to treat herpes. But that's about it. Since those days, the HIV community's ability to mount demonstrations has faded, perhaps in direct proportion to the reduction in AIDS deaths because of the success of newer and better therapies. Unfortunately, those therapies are more expensive than ever.

A new strategy comes to the forefront

Starting with the launch of the drugs Ziagen (abacavir) and Sustiva (efavirenz) in 1998, a different approach has been employed. People from several community groups banded together under the ad hoc name of the Fair Pricing Coalition and developed a process for working with manufacturers to influence the price of new drugs by working with them before the drugs are approved and the price is announced. Though the success of this process varies with each drug, it has often been a very productive process that helped keep the price of drugs from getting even higher than they are.

The first goal of the Fair Pricing Coalition is get each company to price its new drug in a way that is "cost neutral," which means that it should not increase the overall cost of treatment of each person who uses it. In practical terms, this requires that new drugs be priced within the range of other drugs of the same type. A new protease inhibitor (PI) should not cost more than other, already approved PIs. A new NRTI should not be priced higher than other similar drugs, and so on.

A secondary goal is to begin to lower the price of drugs, but so far, this has only been possible in developing nations, which get the lowest possible prices. Unfortunately for us, the cost of new drug development (and company profits) come almost exclusively from the prices charged in the US, Canada, Europe and Australia. Who pays the very highest price varies from one drug to another and one country to another. Because European countries typically engage in some type of price controls, popular belief is that the US always pays the highest price. However, this is not true and sometimes, the highest prices are found in a European countries. There appears to be little rhyme or reason to how this occurs. For more information on the Fair Pricing Coalition and how it operates, see the article, *"What is the Fair Pricing Coalition?"*, on Project Inform's website.

Some background on pricing

As straightforward as "$29 a day" might sound, the actual "price" of a drug is much more complicated. There are several different prices for each drug, and different ways of expressing those prices. In the US, the two most common ways of stating drug prices are the "WAC" price (Wholesale Acquisition Cost) and the "AWP" (Average Wholesale Price). Neither one, though, is a real price that anyone pays, nor are they what their names imply. Rather, they're standardized ways of expressing a price in a uniform way, thus allowing comparisons to be made from one drug to another.

For the sake of simplicity, it is generally accurate to say that the WAC price is 4/5 of the AWP, or put another way, the AWP is about 25% higher than the WAC price. In addition, there's a Medicaid price and an ADAP (AIDS Drug Assistance Program) price and a VA (Veterans Administration) price. Some, like the Medicaid price and the VA price, are closely guarded secrets and cannot be publicized by law. All of them, however, start from the WAC price, from which discounts or rebates and supplemental rebates are negotiated to reduce the actual cost. Government is technically forbidden from negotiating over prices with drug companies for some of these, while negotiation is routine for others. In some cases, like ADAP, there is a standard discount from the WAC price that is required by law and state ADAP groups can negotiate supplemental rebates to lower the price further still, but this can only be done after the original price is set.

As if this isn't confusing enough, with some drugs even the WAC price doesn't fully reflect the starting point for pricing negotiations because some drugs cannot be used alone. The most common example of this is the class of drugs called protease inhibitors. Today, almost all PIs must be used with a "booster dose" of Norvir (ritonavir), another PI that is almost never used alone, but which

plays a critical role in helping other PIs to work. Without it, most of them aren't worth taking. So if you ask what the real price of using a new protease inhibitor will be, in most cases you will need to add in the cost of the particular boosted dose of Norvir. While the Norvir booster is a different drug, the new protease inhibitor cannot be used without it, so their costs can logically be combined.

We're not done yet though because the price of the add-on booster, Norvir, has a highly varying cost depending on how a person takes it. A few years ago, Norvir's manufacturer raised the AWP price of Norvir by 400%, in their view to compensate for its reduced use as a booster instead of it being used as a primary drug. But this horrendous price increase only applied to people who got the drug through private insurance or bought it out of pocket (something very few people do). The old AWP price, which first had to be converted to the WAC price, stayed in effect for people who took Norvir under Medicaid or ADAP programs. And in a final step, the ADAP Crisis Task Force negotiated further reductions in the price of the Norvir booster, with the effect that for the ADAP program at least, Norvir costs less today than it did four years ago under the old price, before the 400% increase.

A new drug gets priced

Now, anyone who's still following this is ready to consider the question, *What is the price of Pfizer's new oral entry inhibitor, Selzentry?* The only information given is that the daily WAC price is $29 per day. Evaluating what this meant and how it compared to other drugs was the challenge faced by the Fair Pricing Coalition team that had worked with Pfizer for several months trying to keep the price as low as possible.

To really understand the price of Selzentry, all of the factors discussed above had to be taken into account, plus one more, very big factor. Before using Selzentry, people need to take a "tropism" test that determines whether they have the kind of virus that will respond to the drug. Some people do; some don't. If people with the wrong kind of virus take the drug, at best they waste someone's money; at worst, it will accelerate the failure of other drugs in their regimens since they will get no help from Selzentry.

The Fair Pricing Coalition team figured that if Pfizer was going to insist on including the price of the Norvir booster used with PIs when making a comparison to those drugs, it was only fair that the cost of the tropism test be considered part of the cost of using Selzentry. This was a critical point because Selzentry doesn't use a Norvir booster, which seems to give it a cost advantage relative to PIs. But that advantage is quickly lost when the cost of the tropism test in added to the price of Selzentry, as it is only fair to do.

Below is the summary of price comparisons made in the Fair Pricing Coalition's evaluation of the true net cost of using Pfizer's Selzentry, compared to the prices of the three newest PIs. The comparisons are revealing and show the complexity of evaluating the price of new drugs. We'll leave it up to the reader to draw his or her own conclusions about the price of Selzentry. The only thing that has changed since the approval of Selzentry is that a second, somewhat less expensive tropism assay has been announced. Because it hasn't been clinically validated, however, it's not possible to predict just yet how much it will affect the sales of Selzentry.

Basic WAC prices of Selzentry and three protease inhibitors, per day (before discounts or rebates):

Selzentry (maraviroc)	$29.00
Aptivus (tipranavir)	$29.80
Prezista (darunavir)	$26.00
Reyataz (atazanavir)	$25.72

The picture changes by adding cost of ritonavir boosting (different for private vs. government payers):

For **private payers**, Selzentry seems like a good deal compared to boosted alternatives, assuming they pay the full price of the Norvir booster. Of course, the real price is further negotiated.

Selzentry	$29.00
Aptivus + 400 Norvir	$64.09
Prezista + 200mg Norvir	$42.15
Reyataz + 100mg Norvir	$34.32

For **public payers** (the price before discounts/rebates for ADAP, etc), the Norvir price is the standard price before the 400% increase in 2005:

Selzentry	$29.00
Aptivus + 400mg Norvir	$36.64
Prezista + 200 mg Norvir	$29.42
Reyataz + 100mg Norvir	$27.43

Then there's the tropism test, estimated costs:

For **private payers**: $1,800–$2,000 (negotiated based on volume, etc.)
For **public payers**: $1,400–$1,600 (to be negotiated)

A person will have to take this test at least once and perhaps more than once. For comparisons, we've used $2,000 for private payers and $1,500 for public payers. Actual price may be lower.

Putting it all together, including ritonavir boosting for the PIs and the Trofile test for Selzentry, for the first year we get the following:

Private payers, 1st year: (before negotiation)

Selzentry	$12,585
Reyataz	$12,527
Prezista	$15,385
Aptivus	$23,393

Public payers, 1st year:

Selzentry	$12,085 (base price, before discounts/rebates)
Reyataz	$10,012
Prezista	$10,738
Aptivus	$13,374

The actual price for public payers will be lower for all the drugs since they will be further negotiated. Their relative positions though are unlikely to change much. All prices can change quickly

when companies make their (usually) annual "cost of living" increases, which average around 5%. Five percent of $10,000 or $12,000 is another $500–$600 dollars each year, which is compounded and thus increases with each passing year.

And that's the real price of Selzentry and its competitors.

Update on Experimental Antiretrovirals

Researchers, doctors and treatment activists often use the term 'pipeline' to refer to the collection of all experimental HIV drugs currently being developed. The 2007 Conference on Retroviruses and Opportunistic Infections (CROI), held in Los Angeles and the International AIDS Society Conference on HIV Pathogenesis Treatment and Prevention (IAS), held in Sydney, Australia, were full of presentations on drugs currently moving through this pipeline. This article reviews some of the most important or interesting presentations in the antiretroviral pipeline.

First Up Selzentry (maraviroc)

Selzentry became the first oral entry inhibitor approved to treat HIV. Selzentry tries to block HIV by attaching to a receptor, called CCR5, or simply R5, which HIV often uses to gain entry into cells. In addition to being the fist drug in its class—referred to as *R5 antagonists*—it is also the first HIV drug which targets a part of an immune system cell rather than the virus.

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

Selzentry at CROI

Researchers presented data from the pivotal phase II/III studies of Selzentry during the *late breaker* session at CROI. The studies, called MOTIVATE 1 and 2, looked at Selzentry in people with extensive HIV treatment experience. Both studies compared Selzentry, taken either once or twice a day, to a placebo. Everyone in the study also took a combination of additional HIV drugs, selected by resistance testing, which is called *optimized background therapy* (OBT).

After 24 weeks, close to twice as many people—around 60% vs. 30%—taking either dose of Selzentry had HIV levels below 400 copies/mL. Not surprisingly, the more active drugs people had in their OBT, the more likely they were to reduce HIV levels to undetectable levels. When people had only one other active drug in their regimen, only 9% of people on placebo reached undetectable levels of HIV, compared to 43% taking Selzentry. If people had two other active drugs, there was a similarly large difference: 19% vs. 52%. When people took three or more other active HIV drugs, there wasn't a big difference between the Selzentry and placebo groups.

One of the most important questions about Selzentry (and other R5 inhibitors) revolves around something called tropism. This refers to which receptors HIV uses to gain entry to a cell. All versions of HIV use the CD4 receptor. But HIV also uses either R5, another receptor called CXCR4 (X4), or both. It has been noted that about half of people's HIV will shift from using mostly R5 to mostly X4 in later stage, more aggressive HIV disease. This has led some to think of X4 HIV as stronger, or more virulent, than R5 HIV which is much more common in earlier disease. But nobody really knows whether the emergence of X4 virus in later HIV and more aggressive disease is a cause of disease progression or a consequence of it.

Activists and researchers have been concerned that blocking HIV from using the R5 receptor might result in HIV shifting to use X4, and possibly bring on a more aggressive form of the disease. Researchers in the Selzentry studies used a test called the Trofile assay to make sure that all study volunteers had *R5 tropic* virus (HIV that uses only R5) at the beginning of the study. At the study's conclusion, it was found that about 2/3 of the people who failed treatment despite receiving Selzentry had shifted to either X4 only or to a virus that can use both (*dual tropic*) or a mixed population (*mixed tropic*). Most often the shift was to either dual or mixed tropic HIV. However, this tropism shift did not seem to result in rapid disease progression, which is the greatest concern. More long-term follow up on people who fail on Selzentry is planned.

There were similar levels of side effects for people taking Selzentry and those taking the placebo, with no signs of any serious drug-specific adverse effects. This will need to be validated by more long-term follow up.

Selzentry at IAS

A study presented during the late-breaker session at the 4th IAS Conference showed that the Selzentry was slightly less effective than Sustiva (efavirenz) when used as part of a HAART regimen for people taking HIV drugs for the first time.

The MERIT study looked at over 700 people with R5-only HIV who had never taken anti-HIV drugs. People were randomly assigned to take either 300mg of Selzentry twice a day or 600mg of Sustiva once a day. Everyone in the study also took Combivir (AZT + 3TC). A once-a-day Selzentry arm was stopped early, due to poor results.

After 48 weeks of the study, similar numbers of people in both arms had stopped taking their combination, but for different reasons. Almost three times as many people taking Selzentry dropped out due to treatment failure. More people in the Sustiva group stopped due to intolerance—mostly neuropsychological side effects associated with Sustiva.

Nearly 70% of people taking Sustiva had HIV levels below 50 copies vs. 64% of people taking Selzentry. Surprisingly, this difference was only seen among people in the study from the southern hemisphere. There were several reasons hypothesized for this difference—different types (clades) of HIV or problems with the R5 screening test—but this finding remains unexplained.

Another somewhat surprising finding was that the people taking Selzentry experienced larger increases in CD4 counts- an average of 169 cells vs. 142. The difference happened mostly in the first 8 weeks of the study. This is consistent with other research on Selzentry and other R5 drugs. For example, a study presented at last year's International AIDS Conference in Toronto found larger gains in CD4 cells among people with X4 or dual/mixed HIV who were taking Selzentry, despite no effect of HIV levels. Some have speculated that this is due to the movement of CD4 cells out of lymph nodes rather than a real increase in the number of cells. Others think this drug might have affects on the immune system independent of reducing HIV levels. More research is needed to understand this important issue.

The differences seen between Selzentry and Sustiva in this study were small, but it must still be seen as a setback. The FDA approved Selzentry for people with extensive treatment experience soon. Only about half of treatment experienced people have R5-only HIV, vs. around four in five people who have never taken HIV drugs. Many people think this makes Selzentry (and other drugs that target CCR5) a more appropriate option for people as first or second line therapy.

This study does not rule out Selzentry for first line therapy, but its failure to match up to Sustiva—one of the most widely used first line drugs—casts a shadow for sure. However, a better understanding of the difference seen between people in the northern and southern hemispheres may change this perception. Additionally, some people may give greater weight to the lower toxicity levels seen with Selzentry and not base their treatment decisions solely on viral load.

There are two outstanding issues about Selzentry. The first is the Trofile test. The test is now required for anyone wanting to start taking Selzentry, since there is no point in using Selzentry in people who have X4 virus. The test is very expensive (well over $1,000) and it is unclear who is going to pay for it. There will be a three-week turn around time for this test as well.

The second issue is the concern that some have over the drug's mechanism. As mentioned this will be the first HIV drug ever to target a component of the immune system, rather than HIV itself. Targeting cell receptors has been done in other diseases, most notably cancer, but it not very well studied. Because the functions of the R5 receptor may not be fully understood, some doctors and others are concerned that targeting it might have unintended consequences. These concerns are reasonable, but there haven't been any signals of such trouble from the clinical trials of Selzentry so far.

The FDA approved Selzentry in August and it arrived in pharmacies in mid September. As expected the drug is approved for use by people with R5 HIV and experience taking HIV drugs.

Isentress (raltegravir): A New Benchmark?

Isentress at CROI:

Following closely behind Selzentry is another entirely new kind of HIV drug called Isentress (raltegravir, MK-0518). Isentress is expected to become the first integrase inhibitor (II) to gain FDA approval. Integrase is an enzyme that is required for HIV to mix its genetic information (called pro-viral DNA) with the DNA inside the nucleus of a cell.

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 (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
	etravirine (TMC-125)
Viramune	nevirapine
NRTI + NNRTI combination	
Atripla	efavirenz + emtricitabine + tenofovir
Entry inhibitor	
Fuzeon	enfuvirtide (T20)
Selzentry	maraviroc
Integrase inhibitor	
Isentress	raltegravir

Data from two large studies of Isentress were presented during the CROI late breakers. These studies, called BENCHMRK 1 and 2, were similar in design to the Selzentry studies mentioned before. Researchers compared people taking Isentress to people taking a placebo—with both groups taking optimized background therapy (OBT) as well. The people enrolled in these studies had extensive experience with HIV drugs and were required to have developed resistance to all three prior classes of drugs. On the whole, they were a somewhat more treatment-experienced group that those in the Selzentry studies.

After 24 weeks, 77% of people taking Isentress had HIV levels below 400 copies/mL, compared to 41–43% of people taking the placebo. The same was seen with a stricter measure—HIV levels below 50 copies/mL—with around 60% for people taking Isentress vs. 33–36% for people taking the placebo.

The researchers looked at how both Fuzeon (enfuvirtide, T20) and Prezista (darunavir) contributed to the outcomes. When people were taking Isentress plus both Fuzeon and Prezista, a remarkable 98% had HIV levels below 400, compared to 87% of people taking the placebo. When they were using either Fuzeon or Prezista, but not the other, still 90% had HIV levels below 400 vs. 55–63% taking the placebo. The biggest difference was seen in people who were taking neither Prezista nor Fuzeon, where 74% or people taking Isentress had HIV levels below 400 compared to only 29% on placebo.

Significantly fewer people (16% vs. 51%) taking Isentress had virus level rebound during study. Two resistance mutations were observed in most of the people who had HIV levels rise while taking Isentress. There was no difference in the rates or types of side effects or lab abnormalities seen in people taking Isentress compared to those on placebo.

Results like this have never been seen in studies looking at heavily treated people with virus resistant to multiple types of drugs. For comparison, in a similar study of the protease inhibitor Aptivus (tipranavir), only around 1/3 of people taking the drug had undetectable HIV levels after 24 weeks (compared to 1/5 of people taking other protease inhibitors). Results this remarkable are bound to change the expectations for treating drug-resistant HIV infection.

Isentress at IAS

There were two important presentations of Isentress at IAS, both from the same study. The study presented had two parts. In the fist part, 40 people who had never taken anti-HIV drugs were randomized into 5 groups. For the fist 10 days, people took either one of four doses of Isentress (100, 200, 400 or 600mg, twice a day) or a placebo alone (called *monotherapy*). People in all of the Isentress dosing arms had significant reductions in HIV levels, averaging around 2.2 logs, or about a 99.8% reduction in HIV levels.

In second phase, about 200 people were again randomized into five groups. In each group, 40 people took one of the four doses of Isentress, or the NNRTI Sustiva. Everyone also took Epivir (lamivudine, 3TC) and Viread (tenofovir). Data from this 24-week study were presented at last year's International AIDS Conference, which showed that people in each of the Isentress arms had faster reductions in HIV levels compared to those on Sustiva. Eventually the number of people in all arms of the study with HIV levels below 50 copies was similar in all groups.

The 48-week data presented here in Sydney was similar to what was seen earlier. Follow-up data were also shown here that Isentress had little to no effect on levels of cholesterol and tri-

glycerides, when compared to Sustiva. There were six treatment failures in this study, five in people taking Isentress and one taking Sustiva. Among the five who were taking Isentress, two had mutations which are known to reduce HIV's susceptibility to Isentress. The others showed resistance mutations to the other drugs in the study, mostly the *M184V mutation* associated with resistance to Epivir.

The other presentation on Isentress concerned something called *second phase viral decay*. In most studies of HIV drugs, two distinct periods or phases of reductions in HIV levels have been observed. An initial steep decline, called fist phase viral decay, is usually followed by a more gradual decline, called second phase viral decay. Data were presented here that showed that in addition to reducing HIV levels faster than Sustiva, Isentress also reduces HIV levels more robustly in the second phase. It is not known what affect this difference will make, but it will be followed closely.

The excitement surrounding Isentress was illustrated well in an earlier presentation, when audience members were asked to choose what new and existing drugs they would choose for a person whose current regimen was failing. Isentress was the most often picked, followed by Prezista. Unlike Selzentry, which will only work for people with R5-only HIV and requires a screening test, almost anyone will be able to use Isentress when it becomes available. It represents an entirely new mechanism of action, so pre-existing resistance will not be an issue. It appears well tolerated and effective, both in treatment experienced people and now in people taking HIV drugs for the first time as well.

In September the antiviral advisory committee of the FDA unanimously recommended accelerated approval for Isentress. While not required to the FDA usually follows the committee's recommendations. A ruling from the FDA is expected in October.

Elvitegravir (GS-9137)

Elvitegravir (GS-9137) is an experimental integrase inhibitor being developed by Gilead. Unlike Isentress, elvitegravir requires a booster dose of Norvir (ritonavir). It is being studied in combination with boosted protease inhibitors in treatment experienced people.

Elvitegravir at CROI

There were two presentations on elvitegravir at CROI. The first presentation was on a study comparing ten days of elvitegravir monotherapy to boosted protease inhibitors. Everyone in the study had documented resistance to at least on protease inhibitor. People were randomly chosen to take one of two doses (50, 125mg) of elvitegravir once daily, or a boosted protease inhibitor. Everyone also took two NRTIS. After 24 weeks, people taking `25mg of elvitegravir averaged a l.7 log reduction compared to 1.2 logs for people taking a PI. More people stopped the study due to adverse side effects in the PI group, compared to the elvitegravir groups.

The second presentation examined the development of resistance to elvitegravir. In a lab, samples of HIV were exposed to different concentrations of elvitegravir until resistance developed. Two distinct mutations developed leading to varying levels of resistance. Somewhat of a surprise was that when the researchers exposed the resistant HIV to two other integrase inhibitors, the HIV remained fully susceptible to the other drugs. Earlier research has suggested that HIV that grows resistant to Isentress will be resistant to elvitegravir. This study suggests

that HIV which develops resistance to elvitegravir might remain sensitive to Isentress. More research is needed to further understand this issue.

Elvitegravir at IAS

There was one presentation on elvitegravir at IAS. The study looked at three doses of elvitegravir (20, 50 and 125mg) taken with 100mg of Norvir (ritonavir), compared to Norvir-boosted protease inhibitors. Everyone in the study also took OBT. At the beginning of the study, Prezista and Aptivus were not allowed. They were allowed later, once drug interactions were understood.

The results were mixed. The lowest dose group in the study was stopped early, due to poor results. Everyone in that group was offered the 125mg dose, in an open label (they know what they are taking) rollover study. After 16 weeks, people taking 125mg of elvitegravir had an average drop in HIV levels of 1.7 logs (~97%) vs. 1.2 logs (92%) for the comparator protease inhibitors. Around 40% of people taking elvitegravir were able to reduce HIV levels below 50 copies. This compares to 40–49% in the studies of Selzentry and over 60% in the Isentress studies.

Elvitegravir requires a low dose of Norvir as a booster. This is similar to most protease inhibitors, especially when used by people with extensive HIV treatment experience. It is the first non-protease inhibitor to require a boost. This means that it will probably need to be used alongside a boosted protease inhibitor, and only by people with extensive treatment experience.

Etravirine

Following Selzentry and Isentress, the next new HIV drug likely to be evaluated by the FDA is etravirine (TMC-125). Etravirine is a non nucleoside reverse transcriptase inhibitor (NNRTI). This class of HIV drugs includes Sustiva (efavirenz), Viramune (nevirapine) and the seldom used Rescriptor (delavirdine). The importance of etravirine is that it can work against HIV that has grown resistant to the older NNRTIs. When HIV develops resistance to one drug, it can sometimes also become resistant to other drugs from the same class. This is called *cross resistance*. The three currently approved NNRTIs are highly cross-resistant. This means that most people have one chance at this important class of drugs, as HIV that is resistant to one NNRTI is highly likely to be equally resistant to the others. Etravirine is different. It was designed to overcome resistance to other NNRTIs.

Pivotal data were presented on the experimental NNRTI etravirine (TMC-125) at the 4th IAS Conference. The DUET-1 and DUET-2 trials compared etravirine to a placebo in people with extensive experience taking HIV drugs and documented resistance to NNRTIs. Everyone in the study took a background combination of anti-HIV drugs contaning Prezista.

After 48 weeks significantly more people taking etravirine in both studies had HIV levels below 50 copies. In DUET 1, 56% of people taking etravirine had HIV levels below 50 copies compared to 39% of people taking the placebo (62% vs. 44% in DUET 2). On average people taking etravirine experienced reductions in HIV levels or around 2.3–2.4 logs, compared to 1.7 logs for people taking the placebo. CD4 cell counts rose on average of 78–89 for people taking etravirine, compared to 64–66 for people in taking the placebo.

Not surprisingly the more active drugs that people were taking in the study, the better their results. People who had no additional active drugs in their regimen, 44–47% taking etravirine had HIV levels below 50 copies, compared to 7–9% on the placebo. The difference grew smaller as more active drugs were available, but etravirine still appeared to add benefit.

Etravirine also appears to work best against HIV that has fewer NNRTI associated mutations. If one or fewer NNRTI mutations were detected at baseline, 60–75% of people taking etravirine achieve HIV levels below 50 copies. If three NNRTI mutations were present, that number dropped to 45%; with 4 down to 25%. When five NNRTI mutations were detected, only 15% of people reached HIV levels below 50 copies.

The most common side effect associated with etravirine in the DUET studies was rash, which occurred in about 17% of people in the two studies. Most rashes were mild to moderate, and rarely (2%) led people to stop taking their treatment. Rash was more common in women, but no association with CD4 count was seen. These are promising results for people who can no longer take NNRTIs due to resistance

Rilpivarine (TMC-278)

In contrast to etravirine, which is aimed at people who have failed on another NNRTI, rilpivarine (TMC-278) is being studied as an alternative to Sustiva and Viramune (nevirapine) for first line NNRTI use. It also works against HIV that is resistant to the older NNRTIs. However, it is highly cross-resistant with etravirine.

There was a significant presentation on rilpivarine (TMC-278) at CROI. A study compared three doses of rilpivarine (25, 75 and 150mg, all once a day) to Sustiva, along with two NRTIs [usually Truvada (emtricitibine + tenofovir)] in people taking HIV drugs for the first time. After 48 weeks, similar reductions in HIV levels were seen in people taking all three doses compared to Sustiva. On average, around 80% of people had HIV levels below 50 copies. There were similar numbers of adverse events in all groups in the study, with fewer rashes and central nervous system side effects reported by people taking rilpivarine compared to Sustiva.

At IAS, data were also presented on the affect of rilpivarine on cholesterol and triglycerides. The study compared one group of people taking one of three doses of rilpivarine to another taking the NNRTI, Sustiva. Everyone in the study was also taking 2 NRTIs—mostly Retrovir (zidovudine, ATZ) or Viread plus either Epivir or Emtriva (emtricitibine, FTC).

After 48 weeks, people taking rilpivarine saw no significant changes in total cholesterol, HDL, LDL, HDL to LDL ratio or triglycerides. People taking Sustiva experienced elevations in total cholesterol, HDL, LDL and triglycerides. No data were presented on body shape changes or other metabolic measures. However, the lack of effect of rilpivarine on metabolic parameters seen in this study is a hopeful development.

The data presented here are a small part of the picture for this drug, which will need to show that it is as potent and durable as Sustiva as well. After many years without any successful new drug development in this important class, the development of etravirine and rilpivarine are welcome. A couple of other new NNRTIs are also being studied in pre-clinical settings.

UK-453,061: another new NNRTI

Preliminary data were presented on UK-453,061, an experimental NNRTI, at IAS. The compound is being developed by Pfizer and does not appear to be cross-resistant with the currently available NNRTIs like Sustiva and Viramune

A short-term, dose-ranging monotherapy study followed 48 people who were randomly assigned to take one of seven different doses of UK-453,061 or a placebo for 7 days. HIV levels were checked

daily for the first week and 6 additional times within 40 days. Drug levels were also measured one day after the last dose.

HIV levels dropped the most in people who received 500mg twice a day or 750mg once a day—1.62 and 1.79 logs respectively. HIV levels began to rise around three days after the last dose of drug was given, returning to baseline after around 20 days. There were few side effects reported in the study. Of particular note was the lack of rash seen in the study—a side effect seen with all other NNRTIs to date. More studies of these two doses are planned.

These data are hopeful but very preliminary. The NNRTI class is widely used, but all of the current drugs have significant drawbacks. Alongside the Tibotec drugs etravirine (TMC-125) and rilpivarine (TMC-278), Pfizer's UK-453,061 offers a renewed sense of optimism for this crucial class of anti-HIV drugs.

Old Targets: NRTIs and PIs

While not generating the kind of excitement that the novel targets garnered, there were some presentations on new drugs from the nucleoside analogue reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) classes that were also of note. Although these drugs don't have close to the potential to shift the way HIV is treated that the integrase and entry inhibitors might, the developments remain important as people continue to need options in these well understood groups of HIV drugs.

There was a presentation about an NRTI called racivir (PSI 5004), being developed for people who have developed resistance to Epivir or Emtriva Everyone in the study was on a failing drug regimen with Epivir, with a specific drug resistance mutation called M184V. A total of 26 people were randomized to switch to racivir while 16 stayed on Epivir. After 28 days, people taking racivir had their viral loads reduced by an average of .4 logs, compared to the people who stayed on Epivir whose viral load went up an average of .13 log. These results just border on being useful and it's possible they could be improved with more knowledge of the ideal dose. There was also a poster presentation on another novel NRTI called nikivir, which is being developed in Russia. The data were from lab studies, so it is too early to know if this will be a viable drug.

Apricitibine

Results from a small phase II study of the experimental NRTI apricitabine were presented at the IAS conference. Apricitabine is designed to work against HIV that harbors a genetic mutation-called M184V- that is associated with resistance to the two NRTIs, Epivir and Emtriva. This drug-resistance mutation is common; effective alternatives for people with this form of resistance are greatly needed.

The double blind study compared two different doses of apricitabine (600 and 800mg, both twice a day) to 150mg of Epivir, twice a day, in people on failing regimens with Epivir. People were randomized either to add one of the two doses of apricitabine, or continue to take Epivir. After 21 days of functional monotherapy, people would switch to the best available combination of anti-HIV drugs, which could not contain either Epivir or Emtriva.

Data were presented from the 21-day, functional monotherapy phase of the study. People taking both doses of apricitabine experienced more significant declines in HIV levels, compared to those taking Epivir. People taking 600mg of apricitabine averaged a .9 log drop in HIV levels, while

people taking 800mg had a drop of around .7 logs. Not surprisingly, people who continued to take Epivir had almost no decrease in HIV levels. There were no serious side effects seen in the study, and no new resistance was detected during this 21-day period. The longer term, second phase of the study is ongoing.

NRTIs are the oldest and most studied type of HIV drug. They are also considered to be the least potent. Historically they have played a supporting role in HIV drug therapy, due at least in part to the lack of alternatives. As more classes of HIV drugs become available, the role of this class of drugs is beginning to be scrutinized. More research is necessary before significant changes to the current structure of HAART are undertaken. For now, a new NRTI that will work against HIV that is resistant to the widely used drugs Epivir and Emtriva is welcome.

Genetic Testing and Ziagen

Results presented at IAS Conference confirmed and earlier finding that a simple screening test can be used to predict whether people are at risk for a serious allergic reaction to the anti-HIV drug Ziagen (abacavir). Ziagen is a component of the two fixed-dose combination pills, Epzicom (abacavir + lamivudine) and Trizivir (abacavir + lamivudine + zidovudine).

Results from earlier research as well as clinical practice have shown that between 5–8% of people will have a serious allergy to abacavir. This is called an *abacavir hypersensitivity reaction* or HSR. Symptoms of abacavir HSR include rash, fever, gastrointestinal upset and malaise. They can range from mild to severe, usually worsen with time and can become serious or fatal, especially if the drug is stopped and restarted.

Previous retrospective studies have shown that people with a genetic variation, called HLA-B5701, were more likely to have this reaction to abacavir. The PREDICT-1 study randomized almost 2,000 people to either take or not take the screening test before starting a HAART regimen with Ziagen. People who tested positive on the screening test were not started on abacavir. Those who tested negative or who didn't take the screening test started HAART regimens that contained abacavir. Suspected cases of abacavir HSR were confirmed using a skin patch test.

Researchers compared the rates of both suspected and confirmed abacavir HSR in people who took the screening test (who tested negative for HLA-B5701) and people who didn't get the test. Almost 8% of people who did not take the screening test had suspected abacavir HSR, compared to 3.4% of people who were given the screening test. More importantly, no one given the screening test had a confirmed case of abacavir HSR compared to around 3% of people who didn't get the test.

It is important to point out that 84% of the people in this study were Caucasian. Research shows that the HLA-B5701 variation is most common among Caucasians. Clinicians have widely reported lower rates of abacavir HSR among people of African and Hispanic origin. Results from a retrospective analysis of HLA testing, called the SHAPE study, found it to be an effective screening tool for people of Asian and Latin ancestry. The sample size of people of African descent was too small to determine the usefulness of HLA testing for this group.

This study has two important implications. First, it shows that HLA screening is very effective at predicting people's risk of abacavir HSR. Secondly it suggests that abacavir HSR is probably overdiagnosed. Use of HLA testing might allow for greater confidence in using abacavir as part of a HAART regimen. This is particularly important as abacavir is considered by most to be one of the most potent NRTIs, along with Viread, and fear of HSR has been a main reason for many people avoiding its use.

Protease Inhibitors

The only new PIs that were presented at CROI were pre-clinical. A poster presentation was made on a compound from Gilead called GS-874 that showed it had a high genetic barrier to resistance and might have less impact on fats and other metabolic markers than other PIs. However, Gilead has since dropped plans for any further development of the GS-874. The other drug was GRL-98065, which shows activity against HIV with a high level of resistance to other PIs.

Comparing Prezista against Kaletra

At IAS, Dr. Valdez-Madruga presented groundbreaking data comparing the protease inhibitor Prezista (darunavir) to Kaletra (lopinavir + ritonavir) in people with extensive treatment experience. After 48 weeks, a significantly higher percentage of people taking Prezista (77–67%) had HIV levels below 500 copies. The same was true when looking at the percentages below 50 copies, with 71% of people taking Prezista compared to 60% of people taking Kaletra achieving these very low virus levels. On average people taking Prezista experienced 30% greater reductions in HIV levels as well. More people taking Kaletra experienced virologic failure compared to Prezista. (Virologic failure is defined as either never achieving HIV levels below 400 copies, or having HIV levels rebound after being suppressed.) Increases in CD4 T cell counts were similar between groups.

The side effect profiles looked somewhat different as well. More people taking Kaletra (42% vs. 32%), had diarrhea, while rash was more common among people taking Prezista. Most of the adverse events in the study were mild to moderate, and few led people to leave the study.

This study is groundbreaking because it is the first head-to-head study of any protease inhibitor compared to Kaletra in which the PI being studied was proven superior to Kaletra. Kaletra has been a preferred PI for some time, due both to impressive durability and an extensive track record in research and clinical practice. Over the past few years, several companies have conducted trials of their own competitor PIs, and been able to show that they were non-inferior. In basic terms, proving non-inferiority means that the two drugs are more or less equivalent.

Proving superiority to Kaletra had never been achieved. Approved in late 2006, Prezista has thus far shown itself to be a potent and effective option for people with drug-resistant HIV. Studies are underway looking at Prezista in people taking HIV drugs for the first time, which are also head-to-head comparisons to Kaletra.

The PI that is garnering the most attention right now is called PPL-100. It merits attention because it is the first new PI in a long time that does not require Norvir boosting. Merck recently bought this compound for development. There were no data presented on it at CROI, but we will continue to follow the development of this drug closely.

Other Drugs in the Pipeline

Uncertainty for vicriviroc

There was a presentation on Schering's CCR5 antagonist vicriviroc (Schering D) at IAS. In this study, 118 people on a failing HIV drug regimen who were shown to have R5-only HIV were randomized to take one of three doses (5, 10 or 15mg) once a day of vicriviroc or a placebo plus the best combination of ARV available to them. The 5mg arm of this study was stopped

early, due to high levels of virologic failure. People in both the 10 and 15mg arms had sustained reductions in HIV levels after 48 weeks of therapy, averaging over a l.5 log reduction.

However, only around a third of people taking vicriviroc in this study achieved viral loads below 50 copies. While this is higher than the 10% taking the placebo, the result is mediocre. Also of some concern is that around 15% of people taking vicriviroc saw their HIV switch from R5-only to X4 or dual/mixed population. There hasn't been adequate follow up on these people, but to date there hasn't been evidence of rapid disease progression associated with this switch, and most people's virus population seems to revert to R5 when they stop taking vicriviroc.

It is fair to say there is some uncertainty about this drug. This is mostly due to the mediocre results from the studies to date. There are also concerns about higher rates of cancers in people taking vicriviroc in this study—although the study's Data Safety and Monitoring Board (an independent group of scientists, doctors and community members who review the results from the study to ensure no harm is done to the study participants) didn't feel like that the study should be shut down.

Another area of concern for vicriviroc and all CCR5 drugs, is the screening test—called the Trofile assay—necessary to determine if people can take this class of drugs. There is a growing concern about the ability of the test to detect low levels of X4 or dual/mixed HIV, which could expose people to a higher risk of treatment failure.

PRO-140

Results were presented at the IAS meeting from a study of PRO140, a monoclonal antibody entry inhibitor that blocks the CCR5 receptor. PRO140 is different from other drugs that target CCR5, like Selzentry and vicriviroc in two important ways. First, unlike these other drugs, PRO140 must be given as an intravenous infusion: through a needle directly in to the blood. Second, it targets a different part of the CCR5 protein, meaning it should still work against HIV that has grown resistant to the oral R5 drugs.

The study followed 49 people who were given a single dose of PRO-140 as a monotherapy. All volunteers had only *R5 only* HIV (HIV that uses the R5 receptor) and had been off all other anti-HIV drugs for at least three months. They were given one of three different doses (0.5, 2 or 5 mg/kg) of PRO-140 or a placebo by infusion. Changes in HIV levels were checked periodically for 60 days.

People given the two higher doses of PRO-140 in this study had significant drops in HIV levels. At the highest dose, the average drop was 1.8 logs. Reductions in HIV levels were greatest 10 days after infusion, and rose back to pre-infusion levels after around 30 days. There were no serious side effects reported in the study, and only one person taking PRO-140 experienced a shift in HIV type from R5-only to dual/mixed HIV.

The magnitude of reduction in HIV levels seen from a single dose was impressive. While the optimal dosing schedule for this drug hasn't been determined, the fact that the lower HIV levels were maintained for so long after infusion suggests that it might be given every 10 days to 2 weeks.

Monoclonal antibodies are large proteins that are expensive to manufacture. With so many powerful, easy-to-use oral HIV drugs available many people question the need for such therapies. However, the results from this single-dose study were impressive enough for the drug to move forward. More studies are planned to start later this year.

The Pipeline: Where Do We Stand?

The 2007 CROI and IAS meetings and the subsequent months were dominated by news on Isentress and Selzentry, and for good reason. They are two effective and well tolerated drugs from entirely new classes. Along with Prezista approved in 2006 and etravirine (likely to be approved in early 2008), this has been a uniquely productive period in HIV drug development, especially for drug-resistant HIV.

What about just a bit further down the line? While it is always difficult to speculate on the pace of HIV drug development, there is little doubt that beyond 2008 there is likely to be a slow down. However, there are many drugs, including some quite interesting ones, in development right now. Well over 100 new HIV drugs are in some stage of development, including 28 in human clinical studies. Most of these are unlikely to pan out, especially the ones in pre-clinical testing. However, some are likely to make it through, and others are being added to the list all of the time. While we may never again see a moment in time like now where so many new and promising compounds come to the end of the development process so close together, but HIV drug development continues.

Flu shots and the upcoming flu season

Influenza, or simply the flu, is a serious respiratory infection that makes hundreds of thousands of Americans ill each year. It can cause many complications for people with damaged immune systems, including people living with HIV. Despite improved prevention and treatment, the flu still causes 36,000 deaths in the US each year. This publication provides an overview of the disease with a focus on preventing the illness.

What is the flu?

The flu virus is quite common, highly contagious and very prone to changing itself. There are three categories of flu viruses: type A, B and C. All three can change into new strains, though type A mutates often and causes most of the illness in the US.

Two important proteins on the surface of the virus readily change, or mutate. These are called *haemagglutinin* (H) and *neuraminidase* (N). Strains of type A are named by the different versions of these proteins. For example, the avian flu virus is called H5N1, because it has haemagglutinin 5 and neuraminidase 1 on its surface.

You cannot develop a lifelong immunity to influenza. Even if you are protected against a flu virus one year, you may not be protected from a new strain the next year.

The flu virus originates in birds and often infects pigs, where it mutates into new strains. This is why new flu shots are required each year. Most Americans get flu shots in October and November. However, the flu season can last as late as May, so getting vaccinated later is a wise choice for some.

Each year researchers try and predict the most likely strains of influenza to hit the US. Sometimes, different strains show up rather than what was predicted. Depending on how serious an illness they produce, new vaccines may be rushed into production. For 2007–2008, the vaccines for the following three strains are available:

- Type A: Solomon Islands/3/2006 (H1N1)-like (new for this season)
- Type A: Wisconsin/67/2005 (H3N2)-like
- Type B: Malaysia/2506/2004-like antigens

How do you get the flu?

The flu virus is highly contagious, which means it's easy to get from someone else. The virus is passed from person to person by breathing in droplets that contain the virus from the air. Other ways include having direct contact with infected fluids from the mouth, nose and eyes or handling items touched by an infected person. This includes kissing, drinking from someone else's glass or sharing hand towels, among many others.

Who is at risk for the flu?

Everyone is at risk for getting the flu. However, people with certain medical conditions, such as heart disease or weakened immune systems or those with respiratory problems, are more at risk. These individuals also have a greater chance for having more severe symptoms. People who have frequent contact with others, such as in rest homes, hospitals, day cares or schools, are also at higher risk.

What are the symptoms?

Many people talk about having the flu when in reality it's just a cold. (The term *stomach flu* is somewhat inaccurate because the flu virus doesn't affect the stomach, though some people may feel it does.) Both illnesses are caused by viruses. Here are some ways to help tell the difference between them.

Colds tend to be less severe than the flu, come on slowly and last only a few days, usually less than a week. Common symptoms are sore throat, sneezing, coughing, runny nose and congestion. Older children and adults rarely get more than a mild fever, if at all.

Flu symptoms usually come on suddenly. They may include a high fever, body aches, extreme fatigue, headache, cough, sore throat and chills. Symptoms start to develop from one to four days after being infected with the virus and often last 1–2 weeks or longer. Headaches may appear at the start of a fever. Stomach problems are rare, but they may occur in young children.

Since the flu can lead to other respiratory illnesses like pneumonia, it's important to seek medical help if your symptoms become worse. This includes having an extremely high fever, a fever lasting more than three days, trouble breathing, symptoms that do not improve or become worse, or a severe headache or stiff neck. Also, if your mucus (the fluid from your nose or chest) becomes bloody or changes color, this may indicate a new condition that needs to be looked at.

How do you diagnose the flu?

In most cases, doctors diagnose the flu simply by the symptoms you have, especially when they occur during a peak flu season. Blood tests (rarely used) and cultures from the throat or nose can be used to identify the virus. Cultures may take up to two days for a result, which may not help your doctor decide on the proper treatment. The *rapid flu test* gives results in a half an hour, though the test is not 100% accurate.

How do you prevent the flu?

Getting vaccinated against the flu before the flu season starts is one of the best ways to help prevent specific strains of the illness. However, some people choose not to get flu shots for various reasons.

Even if you do get one, there are many ways to reduce your chances of getting the flu. For more information, read the section *What about flu shots?* below.

One simple and effective way is to wash your hands with soap and warm water regularly. If they're not available, using hand sanitizers with alcohol can keep your hands clean. Since the flu is passed through the air, avoiding crowds and contact with people who have the flu will help. Also, avoid people who sneeze and cough.

Keeping your hands away from your face will also help reduce the number of infections. Infections often occur when you touch your hands to your mucus membranes, like those in your mouth, nose and eyes.

Another way to prevent infection is by not coming into contact with surfaces that others have touched, especially in public areas like a bus or restroom. Handling toys, handrails, doorknobs, phones, counters and even money that was touched by someone with the flu can expose you to the virus. Some people go as far as using a paper towel to turn off the tap and open a public restroom door.

How do you treat the flu virus?

Taking medicine to prevent or reduce the severity of the flu is called *chemoprophylaxis*. Two drugs are used this way, called *neuraminidase inhibitors*: Relenza (zanamivir) and Tamiflu (oseltamivir). Relenza is inhaled through the mouth. Tamiflu is taken by mouth as a capsule or as a powder for drinking. Relenza has been safely tested in older children and adults. Tamiflu has been studied in adults and infants over one year of age.

Very little data exist on using either drug in people with HIV. However, using them may help control the spread of the flu during an outbreak. One six-week nursing home study of Tamiflu found the flu was reduced by 92% among its residents. In other studies, the risk for getting bacterial or viral pneumonia—common and dangerous complications of the flu—was reduced by half for those taking Tamiflu compared to placebo. Symmetrel (amantadin) and Flumadine (rimantadine) have also been used this way.

It's important to work with your health care provider to decide if and when chemoprophylaxis is right for you. The CDC recommends close monitoring while taking these medicines. And, if a person has frequent contact with the public, a doctor may prescribe this type of drug during the two weeks after being vaccinated. This helps protect a person while the vaccine creates antibodies to the flu.

How do you treat flu symptoms?

Treating the flu also means reducing your symptoms and making yourself feel comfortable. Taking medicines will not rid your body of the virus, but they can help improve your symptoms both for how much and for how long you feel them.

If you think you may have the flu, stay home, get enough rest, and check with your health care provider as needed. If you go to a clinic, emergency room or doctor's office, tell the receptionist that you may have the flu and ask for a mask. This helps reduce passing it onto others.

Getting enough rest is important for recovering from the flu. Drinking plenty of fluids will help replace those lost from a fever. Drinking various drinks like water, fruit juice, and clear soups or warm drinks like tea with lemon are all good choices.

To relieve fever, body aches and headache, taking *acetaminophen* or *ibuprofen* helps. Sponging your body with lukewarm water can also help reduce fever. For a stuffy nose, breathing moist air from a hot shower can help. Using a decongestant or nasal spray with *phenylephrine* in it can help clear or dry up a stuffy nose. If your nasal drainage is thick, the ingredient *guaifenesin* may help keep it thin. Antihistamines are discouraged as they do not treat flu symptoms and may even make your drainage thicker. As with all medicines, follow the directions for their use or talk to a pharmacist.

Cough drops or plain, hard candy can help ease coughing. Over-the-counter medicines with *dextromethorphan* in them can help ease a dry, hacking cough. Beware of cough medicines since some have a high content of alcohol. If you have difficulty sleeping, raise your head at night with an extra pillow if coughing or stuffy breathing keeps you awake. Avoiding smoking and breathing secondhand smoke will also help you breathe.

Some people believe taking antibiotics will help treat their symptoms or cure the flu. Antibiotics are used to treat bacterial infections, not viral infections like the flu. However, they may be used to treat a bacterial infection at the same time as the flu.

Concerns for people living with HIV

HIV kills or damages cells in the body's immune system. This impairs the body's ability to fight infections, like the flu or common cold. People with HIV are more likely to get complications from the flu, such as pneumonia. They are also at higher risk of dying from the flu. Therefore, people living with HIV are considered a priority group to get a flu shot in order to prevent or lessen complications from the flu, particularly heart and lung problems. HIV levels may increase during the four weeks after getting a flu shot. If you're living with HIV, plan your routine blood draws and flu shots carefully.

Concerns for pregnant women

It's important to prevent the flu during pregnancy, as it can last three times longer in pregnant women. Being pregnant can also increase your risk for getting other complications from the flu, such as pneumonia. However, catching a cold or the flu during pregnancy rarely causes birth defects.

The best way to prevent the flu is by getting a flu shot, and by following the personal habits described in *How do you prevent the flu?* above. The flu shot is safe to get while you're pregnant, though it may be wise to get it before becoming pregnant since some women feel fatigue and muscle aches from the shot. The flu shot is also safe to get while you're nursing. However, getting the *nasal flu vaccine* is not recommended as it's a live virus and has not been tested in pregnant women.

Many flu and cold medicines have not been well studied in pregnant women. Some flu medicines to avoid during pregnancy include Tamiflu, Flumadine, Relenza or Symmetrel. These drugs may cause a small increase in the risk of birth defects. Taking aspirin may cause bleeding. Taking ibuprofen hasn't been studied in pregnant women. Acetominophen is the recommended medicine for pain and fever. Women should check with their doctors before taking any over-the-counter or prescription medicine when they're pregnant.

Concerns for children and people over 50

Both influenza type A and B have been linked to *Reye's Syndrome*, a possibly fatal complication that usually affects children under 18. The risk for the condition is increased when taking aspirin. It's strongly recommended that children should not take aspirin products during a viral illness like the flu or chickenpox.

Children under 6 months of age should not get the flu vaccine. Cough and cold medicines should not be given to children younger than two unless a doctor has said so. If your child's doctor tells you to give a medicine, be sure to follow what he or she tells you to do.

What about flu shots?

Getting a flu shot will help protect and/or reduce the symptoms of specific strains of the flu. It takes about two weeks for your body to become protected by making antibodies to it. Some people may feel fatigue and muscle ache from the shot. Flu shots do not give you the flu.

People with CD4 cell counts below 200 may have a weaker antibody response to a flu shot. However, many experts still recommend those at high risk for flu complications get vaccinated.

The Centers for Disease Control (CDC) recommends flu shots for the following people at high risk for complications from the flu:

- children six months to six years old;
- pregnant women or women who are planning a pregnancy during flu season;
- people with chronic medical conditions such as diabetes, asthma, heart disease and HIV/AIDS;
- people 50 years and older;
- people who live, work or volunteer in health care facilities; and
- people with close contact with someone in a high-risk group.

Some people are not recommended to get a flu shot, such as those with a severe allergy to hens' eggs or a history of onset of *Guillain-Barre Syndrome* shortly after getting another vaccination. It's recommended that people living with HIV (or other immune suppression) should not get the live virus flu vaccine sold as *FluMist*. Although no firm data exist, some recommend avoiding close contact for two weeks with those who have taken FluMist to avoid possible exposure to the live virus. In general, healthy people between 5 and 49 years of age can use FluMist.

A flu vaccine clinic locator is available online from the American Lung Association. Visit *www.flucliniclocator.org* to enter your zip code and date and then receive information about clinics scheduled in your area. For more information about the flu and living with HIV, call Project Inform's HIV/AIDS Treatment Information Hotline at 1-800-822-7422.

Reyataz Monotherapy Study Stopped

As reported in the April 2007 issue of the journal, *AIDS*, a study examining the use of Reyataz (atazanavir) as monotherapy was stopped early due to high rate of virologic breakthrough. The researchers planned to study 30 people, with undetectable HIV for at least one year on conventional HAART. They would be switched from their regimen to a once-a-day regimen of 300mg of Reyataz + 100mg of Norvir (ritonavir). The study was halted after 15 people were recruited because there were 5 cases of rebounding HIV levels. The five cases of viral rebound happened between 12 and 16 weeks after starting Reyataz monotherapy.

The researchers looked to see if there was a connection between levels of Reyataz measured in the blood and the risk of viral rebound, and found none. They did find a connection between levels

of bilirubin (a protein found in blood) and the risk of failure. The authors argue for more research to understand the connection between bilirubin and treatment outcomes with Reyataz.

There has been some interest among researchers in studying certain anti-HIV drugs as possible monotherapy. This interest stems largely from Dr. Joel Gath's research on Kaletra monotherapy—which found it to be fairly successful, but not as much so as conventional HAART. Reyataz drew interest due to the combination of its potency and its high barrier to resistance. This study suggests that the risk of early virologic breakthrough on Reyataz monotherapy is unacceptably high.

Dutch Study Finds Treatment Interruptions Safe for Some

A study published in the April 2007 issue of the journal AIDS found treatment interruptions to be safe in people who began anti-HIV drug treatment for the first time when their CD4 counts were above 350. This finding is at odds with other studies of treatment interruptions—most notably the SMART study, but also PART, DART and TRIVICAN—which all found treatment interruptions to be risky. The difference may be due to the groups of people being studied.

Researchers looked at people from the ATHENA cohort, which includes all HIV-infected people getting care in the Netherlands. To be eligible people had to be on stable antiretroviral treatment for at least one year, have undetectable HIV at the start of the study and, most notably, had to have started taking HIV drugs for the first time with CD4 counts above 350. Other research has shown that treatment interruptions are riskier for people whose CD4 levels have been low at some point. A person's lowest ever CD4 count is called a nadir CD4.

In this study, 71 people were given the choice whether to stop or continue taking their anti-HIV drug regimens. A total of 46 people chose to stop, while 26 decided to continue. After 48 weeks, 5 (11%) of people in the group who interrupted treatment restarted, none because of illness. After 48 weeks, people who stopped their treatment saw HIV levels rise to pre-treatment levels, but their average CD4 count remained 85 cells above pre-treatment levels. Nobody had CD4 counts dip below 300. Researchers also looked at measures of quality of life, and found no significant differences between the groups.

Due to SMART and other studies, the trend has been decidedly negative for treatment interruptions of late. These results seem to suggest that treatment interruptions might be safe for those who started anti-HIV therapy with high CD4 counts. Importantly, it found no quality of life benefit or cost to interrupting treatment.

It is important to note that this was a small study, and almost 86% of the people studied were men. It was also not a randomized trial, as participants were able to choose whether to stay on or interrupt treatment. The results of non-randomized trials are considered less reliable than randomized ones. This study suggests the need for more research on treatment interruption in people whose immune systems have never been significantly damaged by HIV.