PROJECT INFORM

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CROI is the annual Conference on Retroviruses and Opportunistic Infections.
For complete online coverage: ***www.projectinform.org/news/09_croi/index.shtml***.

NEWS ON MEDICAL PREVENTION STRATEGIES

Testing PrEP on a global scale

In her opening plenary at CROI 2009 in Montreal, Canada, Dr. Sharon Hillier from the University of Pittsburgh School of Medicine highlighted the possible dramatic impact that using PrEP (*Pre-Exposure Prevention*), if effective, could have on the world's HIV epidemic, along with some of its possible disadvantages. PrEP is using HIV drugs (either as a pill or as a gel or cream, vaginally or rectally) to prevent HIV infection in non-infected individuals.

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The potential promise of PrEP

Given the breadth of global resources being used to treat HIV disease today, it's becoming clearer that alternative solutions to the AIDS crisis must be found. So far, potent HIV therapy has extended the lives of millions of people, but with it comes challenges, such as the need for lifelong therapy or the swelling costs of global health care, to name just a couple. Medical prevention strategies such as PrEP (as opposed to behavioral strategies such as negotiating safer sex) could be one avenue to curbing escalating infection rates and reducing the consequent burden of HIV disease on health care settings around the world.

This year, CROI 2009 presented data on many PrEP-related research projects, in both humans and animals. The buzz surrounding this topic, especially from the animal data, reflects the hope that this area or at least its investigation may one day lead to advances that turn the escalating rates of infection around. But what is PrEP and why is it getting so much attention? The following is an overview of the current PrEP landscape.

What is PrEP?

PrEP is using HIV therapies, *before* an exposure to HIV, in hopes of preventing HIV infection. It might be taken as a pill or applied topically in a gel or other substance. These products could be applied to the vagina or rectum as a lubricant or spermicidal jelly. The intent for using PrEP is to reduce HIV infection by taking medicine daily or intermittently, *before* a sexual event. So far, one or two HIV drugs have been used in studies. In these studies, PrEP is given to people along with targeted prevention counseling, encouraging them to continue using other forms of prevention such as condoms and other risk reduction practices.

Current studies of PrEP

Animal studies and one early study in women have provided the groundwork for eight major ongoing PrEP studies in humans. One notable animal study (rectal transmission in macaques), compared four regimens in 18 animals with various doses of Viread (tenofovir) with and without Emtriva (emtricitabine) to 18 control animals. One of the regimens with Truvada (tenofovir + emtricitabine) given by injection showed 100% protection against sHIV infection, which satisfied a proof of concept leading to human study.

A West African PrEP study (2004–06) involved 936 women who took 300mg tenofovir or placebo daily. Although this study could not show Viread's effectiveness, it did provide information on its side effects in uninfected people and on *risk compensation*, which is when a person adjusts his/her behavior in response to a perceived change in risk. At least in this study, using PrEP did not increase a woman's risk for HIV infection.

Eight human studies are ongoing or planned where PrEP is given orally. In total, they're studying nearly 21,000 people in various settings. More than half the study volunteers will be high- and low-risk women, as the need for proven woman-controlled prevention methods like PrEP is well past due. The PrEP study landscape also includes researching other primary areas of transmission such as in men who have sex with men (MSM), heterosexual men, injection drug users, and couples with mixed HIV status.

The eight studies include:

US tenofovir extended safety study

This study includes 400 HIV-negative MSM in three US cities. In addition to collecting information on PrEP side effects, other data such as access to HIV care, drug resistance and health outcomes are being examined among those who become infected in the study. It started in early 2005 and will end later in 2009.

Bangkok tenofovir study

This study includes 2,400 HIV-negative injection drug users. It's a randomized, double-blind study comparing tenofovir to placebo.

Botswana Truvada study

This phase II/III study is comparing the use of Truvada (tenofovir + emtricitabine) to placebo in about 2,000 heterosexual men and women aged 18-39. Endpoints include documented cases of HIV infection, adverse events, risk behaviors and adherence issues. The study started in early 2007.

iPrEX

This global study will enroll about 3,000 high-risk MSM and compares daily PrEP of Truvada to placebo. Endpoints include documented cases of HIV infection, adverse events, metabolic changes to bone and blood fats, risk behaviors and adherence, or a person's ability to take the therapy daily as prescribed.

Partners PrEP

This African study will compare once a day Viread, Truvada and placebo in 3,900 heterosexual couples with mixed HIV status. Endpoints include documented cases of HIV infection and safety.

FemPrEP
This phase III African study will follow 3,900 women at high risk for HIV infection and will compare daily Truvada and placebo.

VOICE
This study is planned to start in early 2009 and will enroll 4,200 women. Four study groups include: 1) taking a tenofovir gel, 2) taking oral Viread, 3) taking oral Truvada and 4) taking either a placebo gel or tablet.

CAPRISA
This fully enrolled study is following about 1,000 women taking either tenofovir or placebo gel in a vaginal application. The gel is applied both before and after having sex.

The drugs used in PrEP

In the studies mentioned earlier, two HIV drugs are being evaluated: Viread (tenofovir) with or without Emtriva (emtricitabine). Taken together as a pill, it's marketed as Truvada and is given as one pill once a day. Viread was chosen as a PrEP drug because it has a long half-life, which means it takes at least 17 hours for half of the drug to clear from the blood. Thus, it exerts anti-HIV activity in the blood for a long time. It also has high concentrations within cells (active up to 60 hours), hopefully improving its ability in block HIV infection when using PrEP. Both qualities are desirable for PrEP regimens since HIV is most vulnerable to antiviral affects during early infection.

Viread has side effects, ones that affect kidney function and bone density in those who take it. These effects are fairly well studied in HIV-positive people taking tenofovir. What's not known is how much of an impact these side effects will have in uninfected individuals, and whether this may deter people from taking PrEP as prescribed. Although Viread is the most studied HIV drug for PrEP, another drug called Selzentry (maraviroc) is also being researched as a possible PrEP drug. Data on its use as PrEP will be forthcoming.

The downsides of using PrEP as prevention

This medical approach to prevention doesn't come without possible downsides. One main concern is a person developing resistant HIV while using PrEP, which impacts not only the individual but others in the community who may become exposed to the drug-resistant virus. Once a person develops resistance to a drug like Viread or Emtriva, he or she may not fully benefit from HIV therapy, or the resistant virus could be more aggressive. Though data from animal models have not shown this to be a significant concern, it's data from the full spectrum of these human studies that will need to be pooled in order to clarify the rate of resistant HIV transmission and what, if any, consequence it may have for people.

Another concern is that PrEP may fuel, rather than curb, the epidemic through more infections. Some individuals will likely see PrEP as a "magic bullet" of sorts and rely upon it as their only form of HIV prevention—and it may fail. Believing one is protected when using PrEP, a person may engage in risky (or riskier) behavior and actually increase his or her chance for getting HIV. Further, a person who becomes infected while on PrEP may believe they're HIV-negative and may engage in risky behavior that puts others at risk. These factors, among others, could fuel the epidemic. However, in large preventive vaccine studies where this is also a concern, this was not a major issue. It's

almost certain that anyone wanting a PrEP prescription will have an HIV antibody test done. In studies, PrEP is given to people in tandem with prevention messaging and encouragement to use other forms of risk reduction while using PrEP.

Yet another concern is the people who are not included in current PrEP studies. These projects are mostly studying PrEP in 18 to 40-year-olds. Many others are excluded from these studies, including people with chronic diseases such as TB or evidence of liver or kidney disease. Women who were recently or are currently pregnant or breastfeeding have been excluded. How PrEP impacts these populations will need bridging studies done to assess its effectiveness.

Final thoughts

A great deal of data has accumulated since 2004 in animal studies of PrEP. This has given way to the voluminous study in human that's currently being researched or scheduled to begin. Although many are anticipating what these data could mean to prevention efforts worldwide, study results answering the question about the effectiveness of PrEP in humans won't be available until 2011 or 2012.

PrEP could be given either in a topical or oral product. Through a gel, PrEP can provide higher concentrations of the HIV drug(s) in genital tissues, which could provide more durable preventive effects. Topical PrEP tends to have fewer side effects than its oral counterpart. Women may also have an easier time using it during pregnancy. Long-acting types of gels as well as possible combination products could also be developed.

In pill form, PrEP may provide possible longer-acting protection from HIV infection. However, it also brings with it more issues for side effects, which may impact a person's ability to use or adhere to it as prescribed. It is, however, slightly easier for a person to control or conceal using a pill to using a gel—which is an important factor for those who have a difficult time negotiating sex.

This type of prevention brings up many issues for health care programs, governments, pharmaceutical companies, and for the individuals who may be the future consumers of the product. A greater collaboration between HIV prevention and treatment programs will need to be developed, along with better access to HIV screening programs. Groups who will most benefit from this intervention will need to be identified. How and who will pay for the products will also need to be addressed.

So is PrEP a magic bullet, as Dr. Hillier remarked, or can it live up to its potential? Simply, will it stop HIV infection in people? Will it replace condoms? Or will it become another instrument in our growing toolbox of ways to prevent and treat HIV? Will it be used only in certain populations or will the data direct scientists to develop products that work for everyone?

Project Inform has been involved in many of these issues through its work in national conversations on PrEP. The National PrEP Working Group is one such collaboration of dozens of entities working to lay the groundwork for implementing PrEP in the US should it be shown to work.

For more information on animal studies of PrEP reported on at CROI 2009, read Project Inform's coverage: "Truvada prevents rectal HIV infection in monkeys" (*www.projectinform.org/news/09_croi/022609.shtml*) and "Topical gel prevents HIV infection in monkeys" (*www.projectinform.org/news/09_croi/022709.shtml*).

NEWS ON APPROVED ANTIRETROVIRALS

Truvada and Epzicom are similar at suppressing HIV

Data from the Australian STEAL study show Truvada (tenofovir + emtricitabine) is equal to Epzicom (abacavir + lamivudine) in their abilities to suppress viral loads. Each of the combination pills had unique side effects, which likely mark the major difference when deciding which therapy to choose.

STEAL enrolled 360 people on stable HIV regimens with 2 NRTIs plus either a NNRTI or protease inhibitor (PI). All had undetectable viral loads for at least 12 weeks at study entry. None were on unboosted Reyataz, had prior hypersensitivity to other HIV drugs, or were positive on an HLA-5701 test, which determines whether abacavir is likely to cause a severe allergic reaction.

Average age of the volunteers was 45 and the study included predominantly white (86%) men (97%). About 17% had been diagnosed with AIDS, length of time living with HIV averaged 10 years, and average CD4 count was around 620.

All continued either their NNRTI or PI, with half randomly assigned to take Truvada and the other half Epzicom. The primary objective of the study was to look at failure to maintain an undetectable viral load. Researchers also gathered information on serious non-AIDS events, bone density levels (BMD), lipid levels and death.

Both Truvada and Epivir were about equal at suppressing HIV levels. Epzicom was associated with more side effects in general than Truvada. Epzicom showed a higher risk of heart disease and more than double the risk for changes in lipid levels. However, Truvada showed a higher risk for changes in BMD with lower density scores found in the hip and spine. Though there were some cases of kidney and liver disease and diabetes in both groups, there were no significant differences between the two combination pills and their risks on these conditions.

Truvada and Epzicom suppress HIV levels and maintain CD4 counts at about the same rate. The decision to choose one over the other would likely come down to possible issues of side effects. Loss of BMD is a concern for many with HIV, so choosing Truvada may put a person more at risk for it. Truvada's side effects in general seem more tolerable than Epzicom's. On the other hand, Epzi-

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) analogue 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)	
Intelence	etravirine
Rescriptor	delavirdine
Sustiva	efavirenz
Viramune	nevirapine
NRTI + NNRTI combination	
Atripla	efavirenz + emtricitabine + tenofovir
Entry inhibitor	
Fuzeon	enfuvirtide (T20)
Selzentry	maraviroc
Integrase inhibitor	
Isentress	raltegravir

com appears to cause more changes in blood fats and more heart disease, perhaps from the abacavir in it. Although abacavir has been implicated as a risk factor for heart disease, it's still unclear whether that's the case. Several studies presented at CROI 2009 show a connection though a few others do not.

NEWS ON APPROVED ANTIRETROVIRALS

Two studies show Kaletra and Isentress similarly suppress HIV, yet have different side effects

Results from two studies show that switching from a stable and effective Kaletra (lopinavir/ritonavir) regimen to one with the new integrase inhibitor Isentress (raltegravir) results in similar (though slightly less robust) levels of HIV suppression, yet improved the levels of blood fats (*lipids*). The percent of people maintaining optimal viral suppression was slightly higher among those on Kaletra in both studies. Side effects were similar between groups, though Isentress did not cause the abnormal lipid levels seen with Kaletra.

The two identical studies (called SWITCHMRK 1 and 2) enrolled 702 people who were on stable regimens with Kaletra. Average CD4 counts were above 400, average age was about 42, and 80% were men. Some volunteers showed resistance mutations for NRTIs, NNRTIs and PIs, and many had extensive therapy experience and had regimens fail one or more times. All were off lipid-lowering drugs for at least 12 weeks before study start.

In both, volunteers took at least 2 NRTIs and either styaed on Kaletra or switched to Isentress. After 24 weeks in SWITCHMRK 1, 81% of those on Isentress and 87% on Kaletra reached undetectable viral loads. In SWITCHMRK 2, 88% of those on Isentress and 94% on Kaletra achieved undetectable viral suppression. At week 12, Isentress showed better results for changes in total cholesterol and triglycerides. As for suppressing HIV levels at week 24, 88% of those on Isentress had reached undetectable viral loads while 94% of those on Kaletra were undetectable. The rate of side effects were similar between the two drugs (Isentress 13% and Kaletra 20%.)

For those who switched to Isentress, the drug was well tolerated with somewhat milder side effects and improved lipid levels compared to Kaletra. Isentress didn't suppress HIV quite as well as Kaletra, though its suppression was similar.

NEWS ON APPROVED ANTIRETROVIRALS

Isentress equal to Sustiva in first line therapy

Results from the STARTMRK study results show that the first-in-class integrase inhibitor Isentress (raltegravir) works at least as well as Sustiva (efavirenz) at suppressing HIV levels. It also showed that using Isentress resulted in higher CD4 counts.

STARTMRK included 563 people who had never been on HIV therapy. Half received Isentress (400mg, 2x a day) or Sustiva (600m, 1x a day) with Truvada (tenofovir/Viread + emtricitabine/Emtriva). At study entry, none showed resistance to Sustiva or Truvada, all had viral loads above 5,000 with more than half above 100,000, and nearly half had CD4 counts below 200.

The study included 19% women and 58% people of color, while the average age was 37 years. Nearly 1 in 5 had a type of HIV different from subtype B, a common type found in the US. The study assessed the number of people who had undetectable HIV and the rate of change in CD4s. Side effects were also studied, including effects on the central nervous system (CNS) and changes in fats/cholesterol levels (called *lipid levels*).

After 48 weeks on therapy, Isentress suppressed HIV as well as Sustiva. Isentress increased CD4 counts higher than Sustiva, but it's not clear if this increase was statistically meaningful. Isentress was, in general, better tolerated. Fewer overall side effects occurred with Isentress than Sustiva and notably there were fewer CNS affects with Isentress. As for effects on the liver in those with or without hepatitis B or C, both drugs performed similarly.

Isentress was developed and approved for use in treatment experienced individuals. However, this study is one of many that are looking at its effectiveness when used in first line therapy. Here, compared against the most widely used NNRTI, Isentress seems to be an equal choice for people starting therapy for the first time.

The decision to choose one strategy over the other would likely come down to concerns about side effects. From this and other studies, Isentress seems well tolerated, but since it's a very new drug we don't know its possible side effects over the long-term. On the other hand, Sustiva has been well studied and its effects on the CNS are well documented and have long been a concern for many. These include sleep disturbances, unusual dreams and trouble concentrating as well as rash, dizziness and diarrhea. Some people tolerate Sustiva very well; many others experience at least some degree of side effects which may affect their adherence. At this point, it may just come down to which drug is better tolerated by a given individual and what side effects a person is willing to live with.

NEWS ON APPROVED ANTIRETROVIRALS

Prezista fares better than Kaletra in first line therapy

Two year (96-week) results from the ARTEMIS study show Prezista (darunavir + ritonavir) superior to Kaletra (lopinavir/ritonavir) at suppressing HIV levels in people taking therapy for the first time. Both drugs are potent protease inhibitors, but these results continue to show Prezista's excellent ability at suppressing HIV over time.

ARTEMIS studied people who had never taken therapy and randomly assigned them to take either once-daily Prezista or once-daily Kaletra along with Truvada (tenofovir + emtricitabine). A self-rated M-MASRI questionnaire was given to the volunteers to rate their level of adherence to their regimens. A person's ability to maintain adherence impacted results on suppressing HIV levels.

A total of 689 people with viral loads above 5,000 enrolled. The study included 70% men, 58% people of color and the average age was 35. At study start, volunteers, on average, had been HIV-positive for about two years, had CD4 counts about 220, and viral levels were 4.86 logs. Treatment failure was defined as:

- stopping therapy for any reason,
- not achieving undetectable viral loads on at least two consecutive visits, or
- showing detectable viral levels on two consecutive visits.

Results at 96 weeks show that 79% of those taking Prezista achieved undetectable viral loads compared to 71% of those on Kaletra. Of those taking Prezista, 82% who were optimally adherent (took their meds as prescribed more than 95% of the time) had undetectable viral loads compared to 78% of those on Kaletra. As for those who were not optimally adherent (below 95% of the time), 76% of those on Prezista were undetectable while only 53% of those on Kaletra were. People on Prezista had more pronounced HIV suppression even when they were less adherent to their regimens.

Diarrhea was the most common side effect, occurring in 4% of those on Prezista and 11% on Kaletra. As for changes in levels of blood fats (*lipid levels*), Prezista also performed better than Kaletra on triglyceride (18% vs 28%) and cholesterol (4% vs 13%) levels.

Factors that affected a better response to therapy included lower viral levels at study entry, older age, race and level of adherence to the regimens. Those who were more adherent to their regimens, who started the study at lower baseline viral loads, and who were not black had better suppression of their HIV. CD4 count at study entry did not significantly affect anti-HIV response rates.

Prezista is the latest protease inhibitor approved by the FDA. Its development focused on overcoming the resistance found in other protease inhibitors in efforts to give treatment experienced individuals a potent option should they need to find a new regimen. Given these encouraging results, it appears that Prezista is also becoming a potent option for those starting on their first HIV regimens.

NEWS ON EXPERIMENTAL ANTIRETROVIRALS

Acyclovir: the next new HIV drug?

Acyclovir, a drug used to treat herpes, shows that it also inhibits HIV during the reverse transcription (RT) step in the virus's life cycle. Two studies looked at how acyclovir affected the RT enzyme, which may pave the way to using the drug to treat HIV infection either on its own or together with herpes therapy.

In the first study, in an attempt to find compounds with novel anti-HIV activity, a team from John Hopkins School of Medicine and Howard Hughes Medical Institute searched through nearly 3000 FDA-approved drugs or other drugs in phase II studies. Twenty were found to have moderate activity against HIV and 18 were selected for this study.

In the lab, CD4 cells were infected with HIV and then exposed to 10 uM of acyclovir. Cultures were also individually exposed to the other 17 compounds. Viral load tests were done to assess the reduction of HIV levels. Other tests were used to confirm whether the RT enzyme was the drug's target. Herpes infection and activity were also examined. Acyclovir, along with the other compounds, was shown to suppress HIV replication.

The second study looked at the activity of acyclovir on HIV in various tissues from the tonsils, lymph nodes, rectum and genital tract, all co-infected with various human herpes viruses. After treating HIV-infected cells with acyclovir, viral loads and RT activity were assessed.

If the cells had both HIV and herpes viruses in them, then acyclovir suppressed HIV reproduction in those cells. Conversely, if the cells didn't have herpes virus in them, then acyclovir didn't suppress HIV. However, when cells infected with herpes virus only were added to treated co-infected cell cultures, then acyclovir suppressed HIV again. This suppression of HIV appears to affect HIV that uses both R5 and X4 co-receptors.

For more treatment and health care information, call Project Inform's toll-free National HIV Treatment Hotline at 1-800-822-7422. HOURS: 10a–4p, M–F

More study is needed to discover how acyclovir interacts with HIV, both with and without the presence of a herpes infection. One main concern here is how acyclovir may affect HIV mutations. For example, when people with HIV are simply treating their herpes and not their HIV, they may actually be on "HIV monotherapy" which may then lead to poorer HIV therapy outcomes. This data comes in light of studies from CROI 2008 (*www.projectinform.org/news/08_croi/020608a.shtml*) that showed using acyclovir in herpes-infected individuals increased the risk of HIV infection.

NEWS ON EXPERIMENTAL ANTIRETROVIRALS

Thin pipeline reveals three possible HIV drugs

Three possible new compounds with anti-HIV activity were highlighted at CROI 2009. The three compounds, from a very thin pipeline of possible new HIV drugs, are all in early safety study. Should any of these show effectiveness at suppressing HIV, it will still be a couple of years before they would find their way to market.

MPC-9055

A maturation inhibitor called MPC-9055 entered study for its safety and tolerability at various doses in healthy HIV-negative volunteers. Maturation inhibitors work at the last stages in the life cycle of HIV, as newly formed HIV exit immune cells. These drugs prevent the creation of HIV's core called the capsid, which protects its genes. This, in turn, leads to the production of non-infectious HIV that could not infect other cells and theoretically not damage the immune system.

A single-dose of MPC-9055 at 1, 2, 4, 8, 16, 32, and 48 mg/kg were given to 55 non-smokers on a fasting schedule and placebo was given to 20 people. The 8mg and 16mg doses were also evaluated to see how high- or low-fat food impacted the doses. Results showed that no serious adverse events or lab trends were found. However, one-third of those on MPC-9055 did experience at least one side effect. These were generally mild and included headache, nausea, diarrhea and stomach pain. Food increased blood-levels of the drug two-fold. A multiple dose-finding study is being planned for HIV-positive volunteers.

RDEA427

Safety information from both animal and human study were made available for a new NNRTI called RDEA427. The drugs in the NNRTI class (see Drug ID chart on page 5) are highly cross-resistant to one another, and like the latest addition to this class, Intelence (etravirine), a new NNRTI will have to overcome these resistance issues.

This study examined the reaction of both wild type and NNRTI-resistant viruses when exposed to the compound. Injections of RDEA427 were given to several types of animals and to 4 humans to check on its safety and activity.

The results showed that RDEA427 has sustained activity against many of the most common viruses resistant to NNRTIs, including the most commonly transmitted mutation to treatment-naïve individuals, K103M. Against K103M, the compound exhibited anti-HIV affect for more than 100 days, and also showed longer suppression of K103M virus than Intelence and the experimental NNRTI called rilpivirine (TMC278). It appears that RDEA427 has equal activity against both wild type

and NNRTI-resistant viruses. However, another virus with a common NNRTI-resistant mutation, Y181C, was not controlled by the new drug, a drawback of Intelence and rilpivirine as well.

No adverse events or significant lab abnormalities were seen in the study. However, a possible drawback to using this compound will likely be due to it requiring an injection for dosing. Though it may only be dosed once a day, a daily injection may still be too much for many to even consider.

OBP-601

Another safety study reported data on an NRTI called OBP-601 a derivative of the FDA-approved NRTI, Zerit (stavudine). A single dose of the drug, called festinavir, was examined for safety and tolerability. Lab results, vital signs and safety were assessed at regular intervals. The study followed 64 HIV-negative men in a placebo-controlled single dose escalation study.

There were no serious adverse events and the drug was well tolerated, although mild symptoms such as fatigue, diarrhea and vomiting did occur among a few people. No abnormal lab results were also seen, and food did not have an effect on the drug's absorption in the body.

The anti-HIV activity of the compound persists longer than other NRTIs in test tube study, including against the common NRTI-resistance mutation, M184V. OBP-601 seems to effectively suppress HIV in both wild type and multidrug resistant forms of the virus. The 100mg dose given once a day provided good suppression of virus for 24 hours and is currently under study to further assess its safety and effectiveness in HIV-positive people.

NEWS ON EXPERIMENTAL PHARMACEUTICAL ENHANCERS

Two newcomers may challenge ritonavir's position as the only booster for HIV therapy

Two companies announced development of boosters, or *pharmaceutical enhancers*, that could replace ritonavir's sole position in that role. These enhancers, when used to treat HIV disease, increase the level of other HIV drugs in the blood, thereby bolstering their potency by increasing the length of time those drugs remain active and at optimal levels to fight HIV.

Currently, ritonavir is co-formulated as a booster with lopinavir and sold as Kaletra, but it's also recommended as a booster for other protease inhibitors to augment their anti-HIV activity. However, ritonavir has a rather long list of troublesome side effects and drug interactions. The prospect of having other boosting compounds to choose from without these confounding side effects from ritonavir would be welcomed by many.

Both companies report that their compounds are not active against HIV, as is ritonavir. Also, while both compounds seem to inhibit the same liver enzyme (P450 [CYP3A]) as ritonavir, their sponsors claim they do this in a more specific way, which they contend will be beneficial at the end of the day. Moreover, it's asserted that these compounds will not affect lipid or glucose levels, which hopefully will result in fewer metabolic changes and fewer cases of elevated blood fats or insulin resistance. Only further study will whether either of these claims is true.

Gilead's GS-9350

Gilead Sciences reported results from two phase I proof-of-concept studies of GS-9350 and theorized on its possible co-formulation with their experimental integrase inhibitor, elvitegravir. Gilead

is positioning GS-9350 to be co-formulated with elvitegravir and their combination pill Truvada (tenofovir + emtricitabine) as a single pill competitor to Atripla. Atripla is currently the only one-pill, once-a-day regimen. Atripla contains 2 NRTIs and 1 NNRTI while Gilead's proposed combination is an integrase inhibitor combined with 2 NRTIs plus the booster.

A single and 14-day multiple dose escalating study compared 18 people taking 50, 100 or 200mg of GS-9305 once a day to 18 people on 100mg ritonavir on the ability of the drug to block P450. The two higher doses performed at equal levels to ritonavir. No one experienced grade 4 adverse events or grade 3 or 4 lab abnormalities. The GS-9305 did not appear to impact fats (*lipids*) or sugar (*glucose*).

In the partially randomized study (GS-236-0101), GS 9350 was given together with elvitegravir and Truvada in 44 volunteers. The regimen was compared to ritonavir + elvitegravir + Truvada at 100 and 150mg doses of GS 9350. The 150mg dose was comparable in effect as ritonavir. The only grade 3 or 4 adverse event occurred in one volunteer.

Gilead is planning to start this year a phase II study of this one-pill, once daily regimen in people going on first line therapy. The company is also planning to study GS-9350 as a booster for several protease inhibitors such as Prezista (darunavir) and has already started lab study of the booster with Reyataz (atazanavir).

Sequoia's SPI-452

In laboratory studies, SPI-452 by Sequoia Pharmaceuticals shows no added HIV activity and comparable activity to ritonavir when combined with 8 protease inhibitors in addition to an HCV drug. Like Gilead's compound, SPI-452 showed strong inhibition of the P450 enzyme.

Phase I of the first proof-of-concept study (0452-001) followed 47 people divided into 6 groups, with each group getting doses ranging from 25–600mg. Phase II included 10 volunteers in each of two arms comparing three different once-a-day regimens: SPI-452 + saquinavir, saquinavir + placebo, or placebo + placebo.

From these two phases of the first study, the compound was considered generally safe though 19 people experienced 1 or more adverse events such as headache, which were usually mild. Based on the results, the 25, 50 and 200mg doses were moved forward into a second proof of concept study in regimens with darunavir and atazanavir. In the second study, 45 experienced 1 or more adverse events such as headache, nausea or diarrhea.

Combining the data from both studies, the company reported that the compound appears to boost the activity of the protease inhibitors Prezista and Reyataz comparable to ritonavir while also being a potent inhibitor of P450. And, like Gilead's compound, SPI-452 seems to have a tolerable side effects profile and does not significantly alter lipid levels.

The results show promise for long overdue competitors to ritonavir. Though these proof-of-concept studies may not result in an actual booster for another year or two, they nevertheless represent a positive step in improving the safety and efficacy of HIV drugs taken today.

NEWS ON OPPORTUNISTIC INFECTIONS

Duration of therapy for treating HBV

The French INSERM UMR-S707 study examined the level of liver fibrosis, over time, among 130 HIV-positive people taking tenofovir for hepatitis B disease (HBV). Fibrosis is the development of an excessive amount of fibrous connective tissue. The most severe fibrosis is *cirrhosis*, or scarring of the liver.

The risk of living long-term with cirrhosis, especially its severe forms, is liver cancer. The French team looked at volunteers upon study entry (baseline) and every 12 months thereafter to determine the stage of fibrosis. Stage 0 is no fibrosis and stage 1 is very minimal. Stages 2 through 4 are more serious, with stage 4 fibrosis being cirrhosis.

The group showed significant decreasing levels of fibrosis after nearly 30 months of tenofovir therapy, which supports a rethinking of how long anti-HBV therapy should last. Among people with stages 0–2, their levels remained stable over time. Among those with more severe fibrosis (stages 3 and 4), there was a steep decline in HBV levels through one year of therapy followed by a slow and stable continued decline through years 2 and 3 on therapy. At least among people with more serious fibrosis, if these data are confirmed by other studies, extended therapy may be warranted.

A separate study looked at the development of HBV resistance to tenofovir over a two-year period. Among 88 people who took tenofovir for two years, 75 had undetectable HBV levels and 5 had persistent, detectable low levels of HBV. Among those 5, no specific mutation conferring resistance to tenofovir was identified. More research is needed to evaluate the long-term use and potential resistance issues with this therapy.

NEWS ON HIV RELATED CONDITIONS

Who is at risk for Non-Hodgkin's Lymphoma?

Eric Engels of the US National Cancer Institute presented on the possible role of abnormal antibody fragments called *immunoglobulin free light chains* in predicting non-Hodgkin's lymphoma (NHL) in people living with HIV. NHL is an AIDS-associated cancer.

The risk for NHL increases as CD4 counts decline, though only a relatively small minority of people with HIV go on to develop NHL. The incidence of NHL has declined since the use of potent HIV therapy in the 1990s. To date, there are no tools to help determine who is at risk for developing NHL. Measuring *immunoglobulin free light chains* may be one such tool.

Engels and his collaborators identified 66 men from the Multicenter AIDS Cohort Study who had developed NHL. They then identified four control groups (men of similar race, age, CD4 count, etc.) who did not develop NHL for each of the 66 cases. Everyone had samples stored from one of two time points prior to NHL diagnosis.

Engels' group found that elevated *kappa* or *lambda* free light chains were strongly predictive, regardless of CD4 count, for developing NHL. Further, these abnormal antibody fragments were present years (in some cases up to five) before the development of NHL. Because the levels were elevated before developing NHL, this marker may be a useful tool for identifying someone at risk for developing NHL. Thus far, there are no data on the impact of potent HIV therapy on the marker or if it can be used in predicting a relapse of NHL.

NEWS ON HIV RELATED CONDITIONS

Ezetimibe lowers cholesterol levels

The AIDS Clinical Trials Group A5209 study evaluated the drug ezetimibe, when used with a common statin inhibitor (pravastatin, atorvastatin, or fluvastatin), for its ability to lower LDL cholesterol levels in people on stable HIV therapy. LDL is *low density lipoprotein* cholesterol, commonly referred to as bad cholesterol. Too much bad cholesterol can increase the risk of clogged arteries, heart attack and stroke. Optimally, LDL levels below 100mg/dL are desired.

In the study, everyone had LDL levels above 130 despite being on a cholesterol-lowering statin inhibitor. Average age of the study volunteers was 49 years while about 3 in 4 were men and 57% were people of color. Average CD4 count was 547 and nearly all had undetectable viral loads.

The study included 44 people who took 12 weeks of therapy with 10mg of ezetimibe or placebo in addition to a stable statin inhibitor therapy. After 12 weeks, ezetimibe and placebo were stopped for 4 weeks. After the fourth week of this "washout" phase, those who had taken placebo were given the 10mg ezetimibe therapy, and those who had been on ezetimibe were given 12 weeks of placebo. The therapy proved both safe and effective in lowering LDL cholesterol.

The study showed that adding ezetimibe with a statin inhibitor resulted in significant decreases in lipid levels, including LDL cholesterol, TC, ApoB and non-HDL cholesterol. More than 60% of participants experienced some degree of side effects, the most common being aches, pains and discomfort. Less common side effects were fever, nausea and vomiting, decreases in neutrophil counts, and increases in bilirubin.

NEWS ON HIV RELATED CONDITIONS

Non-AIDS defining cancers in people with HIV

Since the availability of potent HIV therapy, cancers not related to AIDS have become more common than AIDS-defining cancers among people with HIV. This is particularly true of cancers with a known infectious cause, such as anal and cervical cancers (caused by the human papillomavirus or HPV), liver cancer (caused by the hepatitis B and C viruses), and Hodgkin's disease (caused by the Epstein-Barr virus). Cancers without an infectious cause, particularly lung and skin cancers, are more common among people with HIV compared to people not living with HIV.

The use of potent HIV therapy impacts the development of infection-related cancers. In a study of over 20,000 people living with HIV in the Kaiser California system, the rate of anal cancer significantly declined once more potent therapies became widely available. A smaller decline in the rate of Hodgkin's disease was seen over this same period.

However, this same decline was not seen among more than 200,000 HIV-negative people of similar age, race and ethnicity over the same time frame—suggesting that the lower rates of cancer are likely due to the wider use and availability of potent HIV therapy and the resulting improvements in immune health. This same anti-cancer impact from taking HIV therapy was not seen in liver cancer.

Among the cancers not believed to be caused by an infectious agent, lung, skin and kidney cancers were higher among people living with HIV compared to their HIV-negative counterparts. Interestingly, HIV-positive men seemed to have a *lower* risk of prostate cancer than HIV-negative men of the same age, race and ethnicity over the 11-year study. There's some evidence that colorectal

cancers may be increasing in people living with HIV in later years. The wider availability of HIV therapy did not make impact the risk of developing these cancers.

This early report helps to further define cancers of concern for more focused research in HIV. Also, stronger immune systems due to HIV therapy may prevent developing certain infection-related cancers, notably cervical/anal cancers and Hodgkin's disease. In addition to routine monitoring of HIV disease, people living with HIV should diligently explore their cancer risks and screen appropriately.

NEWS ON HIV RELATED CONDITIONS

Limb fat wasting improves with rosiglitazone therapy

The drug for treating diabetes, rosiglitazone (ROSI) improved lipoatrophy and insulin levels in people not taking thymidine NRTIs, which include Retrovir (AZT, zidovudine) or Zerit (d4T, stavudine). ROSI works by increasing the activity of a specific cell protein (called *PPAR-gamma*) that helps to break down fats in the body. Thymidine NRTIs significantly inhibit PPAR, and thus can cause changes in fat distribution, such as fat loss, called *lipoatrophy*.

This double-blind study followed 71 people with lipoatrophy. All stopped their NRTIs at least 24 weeks before study entry, although the average length was 4 years. They were randomized to take either 4mg ROSI twice a day or placebo for 48 weeks. DEXA scans (to measure fat content and bone density) and fasting metabolic tests (to measure insulin levels) were done throughout the study. Facial fat loss was not evaluated in this study.

Women made up 17% of the study participants, average age was 50 years, and 51% were white. About 92% of people had viral loads below 400, and characteristics at study entry were similar between the groups. Average limb fat was ~6500g for ROSI group and ~6400 for placebo. Volunteers could display some amount of insulin resistance, but those with diabetes were excluded from the study.

The results showed that the ROSI group had more significant increases in limb fat on average by 911g vs. 253g on placebo. The percentage of gained limb fat was also higher in ROSI group at 15% vs. 5% on placebo. Triglycerides and cholesterol levels did not change significantly within or between the groups. As well, lipid levels and bone density were not affected by ROSI therapy. According to the researchers, ROSI significantly improves lipoatrophy in people not on a thymidine NRTI. Though ROSI may be a promising therapy for improving lipoatrophy, people on thymidine NRTIs may do best by changing to a regimen without these NRTIs before adding ROSI therapy to their HIV health care.

NEWS ON HIV RELATED CONDITIONS

A person's modifiable risk factors nearly double their risk of non-AIDS death

Data from the D:A:D study showed that factors which people can change and influence nearly double the risk of non-AIDS death. These medical and lifestyle issues include smoking, high blood pressure and diabetes.

The D:A:D (Data collection on Adverse events of anti-HIV Drugs) is a large observational study examining the safety of HIV drugs and health outcomes of those on therapy. Just over 33,000 people were enrolled. Average age was 39, most were men (74%), 45% were white, more than half were

either current smokers or had smoked, 34% had HBV or HCV disease, and 3% had diabetes. At the start of the study, about 3 out of 4 were taking therapy. Average CD4 count was 408 and average viral load was 1,000. The length of time on HIV therapy averaged just over 3 years.

People were evaluated from the time they entered the study until their last follow-up visit (or death) through October 2007. Body mass index (low weight), blood pressure, diabetes, smoking, use of therapy, and current CD4 counts and viral loads were studied.

A total of 2,192 deaths occurred during the period studied. Underlying causes of death included AIDS (32%), liver disease (14%), non-AIDS cancers (12%), heart disease (11%), bacterial infections (9%), non-natural deaths (9%), and other causes (13%.) The results showed the following:

- Lower CD4 counts were associated with a higher risk of death from all specific causes of death.
- Higher current HIV RNA was a risk factor for AIDS-related and liver-related deaths overall and doubled the risk due to AIDS.
- HIV levels above 400 when on therapy raised the risk of death from all causes while HIV levels above 10,000 when off therapy greatly raised the risk for all causes of death.
- Diabetes was associated with all specific causes of death except non-AIDS cancers.
- Smoking was a risk factor for heart disease and non-AIDS cancers.
- HBV and HCV co-infection were related to liver-related deaths, and HCV raised the risk of liver-related death nearly 4-fold.
- Low body weight correlated to a 3-4 times higher rate of death and non-AIDS cancers.
- Hypertension was a 2-3 times higher risk factor for liver-related and heart disease deaths.

Many of these, if not all, are not radically unknown risks for death in the general population let alone people living with HIV. However, the degree to which these factors increase the risk of death in HIV-positive people is striking. Given that people, with or without HIV, can make constructive changes to impact some of the issues that increase risk of death, it's important for people to take a proactive role in addressing what they can to prolong and improve their quality of life.

Changes that people may do to reduce risks include:

- Get tested for HBV and HCV. If you test positive for HBV or HCV, discuss your options with your health provider and follow through with a treatment plan.
- Get the HBV vaccine if you test negative and haven't already had the disease.
- Ensure your current HIV therapy is working as well as it can at keeping your CD4s as high as possible and your viral load undetectable for as long as possible.
- Get routine lab work done and go to scheduled appointments.
- Improve and maintain proper adherence to HIV drugs and meds for other infections.
- Explore smoking cessation programs and stop smoking.
- Eat a balanced diet low in saturated fats and sugars.
- Watch weight and nutrition with the same careful eye as CD4 counts and viral load. Any unplanned weight loss is undesirable (regardless of whether or not it's welcomed).
- If you're diabetic, keep diabetes under control with the proper medications and check-ups.
- Find ways to lower your stress level and to exercise at the level you can.
- If you have high cholesterol, consider lipid-lowering drugs or HIV therapy that has fewer documented effects on lipid levels.
- Consider ways to build more lean body mass.

News briefs from 2009 CROI ...

For complete coverage on these topics, go to *www.projectinform.org/news/09_croi/index.shtml*.

Smoking nearly triples the risk of death

It's well documented that HIV-positive people smoke more on average than HIV-negative individuals. Figures point anywhere from 47-70%, while the national average hovers around 20%. Results from the five-year FRAM study showed that current smoking, as well as older age, significantly increased the risk of death in people living with HIV. Although the study examined many factors related to disease progression and death, the one that was most notable was smoking. Smoking contributes to heart and lung disease and cancer, among many other conditions.

A common blood product called IVIG may help clear the HIV reservoir

Early findings detailed a small proof-of-concept study using high-dose IVIG to reduce the amount of HIV found in resting cells, sometimes call the *latent reservoir*. These reservoirs are compartments of HIV infection, seemingly untouched by conventional HIV therapy, that are believed to harbor the virus that eventually causes people to progress in their HIV disease. The small study enrolled 9 people on effective HIV therapy for 5 or more years who had undetectable viral loads for more than 1.5 years. They were given 30g IVIG daily for 5 days. Lab work, which included identifying the genetic types of HIV in latent reservoirs and blood, was done before and after the IVIG therapy. Seven out of the 9 showed lowered or undetectable virus particles in these reservoirs 8–12 weeks after IVIG. On average, latent HIV was reduced by 68% in the 7 patients who showed a response to the IVIG.

Successful therapy may still lead to loss of kidney function

The SCOPE study showed a loss of kidney function in people with HIV, even in those with well controlled HIV levels on potent HIV therapy (HAART). HAART helps control kidney function, more so than in those with uncontrolled HIV, but some still experience a higher rate of kidney dysfunction. Loss of kidney function was more associated with viral levels than with CD4 counts. The researchers offered that continued control of HIV levels without viral blips is key to maintaining good kidney function over time. However, they did not assess the impact of kidney-toxic drugs in HIV regimens on these findings. Those without HIV control, not on HIV therapy, fared worst among the four groups.

Cancer rate for Isentress similar to other HIV meds

Study data showed that people using the integrase inhibitor Isentress (raltegravir) developed similar rates of cancer as seen among people taking Sustiva or placebo. Cancer rates observed in 4 earlier studies of Isentress had raised concerns. A large analysis of 5 randomized, double-blind studies of the drug eases concern about cancer risks associated with its use.

Risk for invasive anal cancer high among HIV-positive people

More sobering news was presented on a serious HPV-related condition in men who have sex with men (MSM) that can lead to anal cancer. Unlike other diseases that have declined in incidence since the advent of HAART, the appearance of this condition (caused by human papillomavirus) has continued to increase. Incidence of anal cancer is 59-times higher among MSM and nearly 7-times higher in HIV-positive women. This reiterates and underscores the rise of cancers with infectious causes among people living with HIV. A great resource for information about these conditions is the website for the UCSF Anal Neoplasia Study at *www.analcancerinfo.ucsf.edu/about/index.html*.