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

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

This issue of PI Perspective reports on Project Inform's coverage of the International AIDS Conference in Mexico City, August 3–8, 2008.

Anthony Fauci lends support to focus on cure

by Paul Dalton

In a fast moving and wide ranging talk at the International AIDS Conference, Dr. Anthony Fauci, the head of National Institute of Allergies and Infectious Diseases at the NIH, gave new hope and energy to the defining call of AIDS activism, 'Until There is a Cure.' While necessarily short of details, the vision that Dr. Fauci presented points the way forward for both the research community and the activist world.

In his talk, "The Future of AIDS Research," Dr. Fauci took a broad approach to priorities for research — and by extension — advocacy. He looked at 6 key areas, all in a brisk 20 minute presentation: pathogenesis, diagnostics, therapy, prevention, vaccines and, finally, the cure.

Pathogenesis

In the arena of pathogenesis (how HIV causes disease), Fauci pointed to the need for a deeper understanding how the virus interacts with an infected person's immune system. He focused specifically on the events of early infection when HIV accomplishes a 'double whammy': seeding compartments of the body to establish a reservoir while simultaneously dampening the immune response by killing CD4 cells. The death of CD4 cells releases substances that weaken the immune response against HIV.

He suggests that this earliest phase of HIV disease as both a time of vulnerability and opportunity. If one was able to intervene during these early events, it might have profound effects on the course of HIV disease.

Fauci also pointed to the promise of cutting edge technologies to speed up the drug development process. As an example, he mentioned the paper published this February in the journal Science in which researchers detailed over 270 proteins involved in HIV replication. Only 36 were previously known to play a role in HIV replication. "This opens up literally scores of potential new drug targets," Fauci said.

The HIV drug development pipeline badly needs this kind of reinvigoration. The current crop of experimental agents holds very little promise for significant breakthroughs in HIV treatment. This is particularly disappointing when seen in the light of recent findings on two of the newest drugs: Isentress (raltegravir) which seems to lower HIV levels more quickly and possibly thoroughly than other drugs, and Selzentry (maraviroc) which appears to have anti-inflammatory properties.

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Diagnostics and monitoring

Dr. Fauci then detailed the important work to be done in research on diagnostics and other kinds of monitoring: the need for effective, low cost diagnostic tools in the developing. One of the significant obstacles to the effective delivery of anti-HIV treatments in the developing world has been the high cost of crucial diagnostic and monitoring tests like CD4 counts and HIV viral loads. Adding to his call for greater work in these areas, Fauci also stressed the importance of reliable and widely available TB tests in the developing world.

Former Project Inform staff member, Ben Cheng, currently working with the DC-based Forum for Collaborative HIV Research, has done groundbreaking work bringing together scientists and other stakeholders in an effort to develop and test low cost diagnostics for use in developing countries. Without these tests, which are a central part of care in the US and other wealthy countries, the full benefit of HIV treatment can not be realized.

Treatment

Dr. Fauci contrasted the breathtaking progress made in HIV treatments against the fact that we continue to lose ground to HIV worldwide. He cited a report published in the July 2006 issue of Journal of Infectious Diseases that found that HIV treatments had saved 3 million years of life in the US alone. He also showed the real progress made in increasing the number of people in middle and low income countries on HIV treatments, growing from just a few hundred thousand in 2002 to over 3 million today.

This good news is blunted, however, by the fact that for every person put on HIV treatment, 2 to 3 become newly infected by HIV. Worldwide, fewer than 1 in 3 people who need these proven treatments have access to them.

This needs to be seen in light of declining interest by the pharmaceutical industry in HIV. As Project Inform recently wrote about, fewer companies are getting into the HIV game, and some long established players are decreasing their involvement or getting out all together.

While pharma as a whole is doing well, the future for its involvement in HIV is grim. Many of the earliest generation of HIV treatments will see their patents expire over the next few years. This will lead to declining HIV-related profits for these companies. Unfortunately, history has shown us it's unlikely to result in lower drug prices for consumers.

New energy and new products can reinvigorate pharma's response to HIV. As mentioned above some of the newer agents have shown hints of game-changing properties. The industry needs to build on these gains and develop the next generation of HIV treatments, ones that overcome some of the potency and tolerability limitations of the current treatments.

Prevention

One of the most widely covered stories here in Mexico City is the overall sense of frustration with prevention efforts. The CDC's 40% upward revision in the number of new HIV infections each year in the US underscores the limitations of current prevention efforts. So does the fact that 2 to 3 times as many people become newly infected as who start treatment worldwide.

New efforts are needed to stem the growing tide of new HIV infections. While no one is calling for an end to older interventions — like condom promotion and needle exchange — new methods are clearly needed.

In memory of ...

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

John Burnside

Del Martin

Recently Project Inform added prevention to our mission. Bringing our 20-plus years of expertise in drug development, treatment and health care policy activism, we will focus on innovative prevention efforts that have a real chance of helping reverse the troubling spread of HIV infection. Two areas we think hold particular promise are the use of HIV drugs for prevention, called pre-exposure prophylaxis or PrEP, and earlier HIV treatment to reduce community level viral load.

Fauci highlighted some of the successes: reducing mother-to-child transmission and needle exchange. He also talked hopefully of PrEP, microbicides and vaccines. While the sense of frustration with persistently high infection rates is palpable, we can and must use this to create a renewed sense of urgency and embrace creative and innovative approaches to HIV prevention.

Vaccines

"When asked why we don't have an HIV vaccine," Fauci stated, "I say, HIV is very different than other microbes." This seemingly simple statement contains some of the truly vexing issues that have hampered the development of a vaccine to prevent HIV infection.

The single biggest hurdle to overcome is the lack of an adequate natural immune response against HIV in most people. Vaccines work by tricking the immune system into mounting a protective immune response. Because very few people are known to generate such a response against HIV on their own, researchers must continuously hunt for the immunologic keys to controlling HIV.

While no magic bullet has been yet found, there are some promising developments. Fauci cited two papers published in the past year or so where researchers reported significant progress toward identifying potential targets for neutralizing antibodies, the gold standard of vaccine development.

This news is particularly welcome right now, in the aftermath of the failure of the Merck vaccine. This widely reported setback reverberated throughout the HIV vaccine world and led Fauci to shut down a large trial of a different vaccine that was built on the same scientific basis.

While some despair at the prospects of ever developing an effective vaccine against HIV, Project Inform supports ongoing, targeted and strategic research toward this end. Scientific progress is often fraught with setbacks and detours. We cannot turn back; however, the need for a vaccine is imperative. Our strength of will needs to match the staggering need for a vaccine.

And finally the cure

Perhaps the most important part of Fauci's talk was his utterance of the word, cure. After years of virtual silence on the prospects for an outright cure for HIV, there's real movement in the search for a cure. As Project Inform's founder Martin Delaney commented, "It's very important that someone of the stature of Tony Fauci is now emphasizing the critical importance of finding a real cure for HIV and not just settling for lifetime maintenance therapy. A few years ago, such a statement was considered heresy. People just didn't want to accept the fact that treatment, however effective, is no bed of roses and can never fully overcome the problem of drug resistance."

Back in 2004, Project Inform correctly identified cure-focused research (along with microbicides and PrEP) as one of the most important areas of HIV research. At the time, few if any major HIV researchers publically held out hope for curing HIV infection, seemingly content with the successes of lifelong maintenance therapy.

To help frame his short, but powerful discussion on the prospects for a cure, Fauci laid out two types of cures: sterilizing and functional. A sterilizing cure is synonymous with 'eradication' or successful elimination of every viral particle from the body — similar to what has been achieved in

Anthony Fauci lends support to focus on cure

some people with hepatitis C. This kind of cure has long been thought of as the only real cure, because of HIV's ability to persist and replicate even after a decade or more of fully suppressive drug therapy. The thinking is that the virus is able to hide out in sanctuary sites and repopulate the body with circulating virus as soon as drug therapy is stopped.

As Project Inform recently wrote about, this thinking is not necessarily correct. While a truly sterilizing cure is certainly desirable, it may not be necessary. What may be needed is what Dr. Fauci called a 'functional cure,' or the ability for an HIV-infected person to live and be healthy long-term without the need of drug therapy.

Fauci proposed a potential model for such a cure that would involve very early and very aggressive HIV drug treatment, possibly along with HIV-specific immune based therapies. In his mind, the best chance for such a cure would be to begin treatment at the earliest possible moment, possibly within weeks of infection.

This paradigm would only work for a small number of people, which Fauci readily acknowledged. People would need to be diagnosed very soon after infection and have access to the aggressive therapies Fauci mentions.

Nonetheless, it would be truly groundbreaking to find a durable cure for anyone living with HIV. Beyond the obvious benefit to the people cured, it would almost certainly point the way toward better control, if not outright cure, of HIV infection for everyone else living with HIV.

While Project Inform has been advocating for more cure-focused research for some years, the impact of Dr. Fauci's talk should not be underestimated. As Delaney put it, "This is the first time a public official has raised the question of whether it will be possible to provide lifetime therapy for tens of millions of people. As Fauci noted, "It's one thing to provide crash treatment programs, but another altogether to sustain them for a lifetime for tens of millions of people."

In a recent op-ed in the International Herald Tribune, award-winning writer Laurie Garrett called the HIV activist and scientific community to task for growing complacent in the face of lifelong drug therapy and all but abandoning the ultimate goal of a cure. As this writer said here, Garrett missed the mark in some of her comments, but also hit on some important truths — most notably that for all of the very real progress we have made in treating HIV, the current paradigm is simply untenable. Having a figure as important as Dr. Fauci calling for and talking hopefully about the prospects for curing HIV infection should provide a great boost to this field. Project Inform welcomes Dr. Fauci's comments and commits to cure-based research advocacy, until there is a cure.

NEWS ON APPROVED ANTIRETROVIRALS

Abacavir controversy continues to brew

by Paul Dalton

The ongoing and deepening controversy surrounding abacavir was one of the main stories at this year's International AIDS Conference. The 'late breaker' sessions, often the venue for the most interesting research data, included four full presentations debating two important questions about this widely used HIV drug: whether abacavir increases the risk of heart attack, and does it work as well as other drugs for people with high HIV levels. While it's fair to say that controversy remains, Project Inform can't help but note a growing cloud of questions surrounding this important HIV treatment.

Abacavir is sold alone as Ziagen and in the fixed-dose combination pills Epzicom (with emtricitabine/FTC) and Trizivir (with zidovudine/AZT + emtricitabine/FTC). Approved in 1999, abacavir is generally considered among the most potent NRTIs, or nucleoside/nucleotide reverse transcriptase inhibitors.

Until recently, concern over hypersensitivity reactions or HSR has held back the wider use of abacavir. The recent success using a simple genetic test called *HLA screening* to successfully predict a person's risk of abacavir HSR has allayed many people's fears. This led the Federal Guidelines panel to upgrade Epzicom from an alternative to a preferred first line treatment in early 2008.

Increased risk of heart disease

A short time after the Guidelines upgraded Epzicom, trouble began brewing. At the Conference on Retroviruses and Opportunistic Infections (CROI) in February, researchers combed through the D:A:D study and found an increased risk of heart attack — called *myocardial infarction* or *MI* — in people taking abacavir. Overall the risk was about 2 times higher, but it grew substantially when people had more pre-existing cardiovascular risk factors, like being overweight, smoking and having a family history of heart disease. Remarkably, this increased risk appeared to be reversed when people had stopped taking abacavir for 6 months.

In Mexico City, another set of researchers reported on data from the SMART study and found very similar results. SMART enrolled over 5,000 people worldwide who were randomly assigned to take HIV treatment continuously (the viral suppression or VS arm) or to start and stop treatment based on their CD4 counts (the drug conservation or DC arm). As reported here, *www.projectinform.org/news/2006/011206.shtml*, SMART was stopped early when researchers noted a higher rate of all-cause death, as well as heart and kidney disease among people in the DC arm.

To better understand the results from D:A:D, researchers examined the SMART data and looked at everyone who took HIV drugs during the study. They found almost exactly the same increased risk of MI among those on abacavir that was found in the D:A:D. They looked at 4 definitions for heart disease and found higher rates for all 4 in people taking abacavir.

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

GlaxoSmithKline, who makes abacavir (and Epzicom and Trizivir), presented an analysis of a group of other studies, called a meta analysis. Overall they looked at results from 54 studies, involving around 15,000 people who took either abacavir or another NRTI. GSK's pooled analysis found low rates of heart attack across the studies, with no differences among people taking abacavir or other NRTIs.

Which is better: Epzicom or Truvada?

The other debate was whether Epzicom works as well as Truvada for people with high viral loads (>100,000). In February investigators working on the AIDS Clinical Trials Group's (ACTG) 5202 announced that early analysis of their data showed higher rates of virologic failure among people taking Epzicom than Truvada. These data were presented publically for the first time in Mexico City.

ACTG 5202 compares 4 HIV drug regimens. Participants are randomly assigned to take either Truvada or Epzicom with either Sustiva (efavirenz) or boosted Reyataz (atazanavir). The study's Data Safety and Monitoring Board (DSMB) — an independent group of scientists who get an early look at study results to ensure that no harm is done to its participants — found higher rates of virologic breakthrough among people taking Epzicom, who had high viral loads before the study. The DSMB decided to 'unblind' that group, and tell everyone what they were taking. The study remains blinded and unchanged for people with low viral loads.

Overall there were 57 virologic failures among people taking Epzicom compared to 26 for those on Truvada. People on Epzicom were 2.3 times more likely to experience loss of virologic control than those taking Truvada. Looking deeper, they examined 4 definitions of virologic failure and found higher rates for Epzicom regardless of definition. Data also suggested higher rates of adverse events (side effects) for people taking Epzicom.

GSK presented their analysis of 6 studies to see if the same thing was seen. These studies included almost 3,000 people taking HIV treatment for the first time. Using the same criteria as ACTG 5202, GSK's team found no differences in virologic failure rates for people with high vs. low viral loads.

The bottom line

The ongoing controversy surrounding abacavir is certainly fueled by these results. Jules Levin, a prominent AIDS activist from the National AIDS Treatment Advocacy Project (NATAP), told Project Inform that he is unconvinced by these negative findings, 'but the damage is already done.'

When the D:A:D results came out earlier this year, they perplexed most people. There was no known biological explanation for this increased risk. In fact, the study's designers were looking to see if Retrovir (zidovudine/AZT) or Zerit (stavudine/d4T) increased the risk of MI. While not definitive, the fact that a second study — looked at by a second set of researchers and presented at a major scientific conference — found the same thing greatly strengthens the power of the observation.

Most of the doctors, researchers and activists we spoke with feel that SMART's confirmation of the D:A:D raises serious issues for using abacavir, particularly by people at high risk for heart disease. The 5202 story is less clear. The finding itself is troubling. If it is independently confirmed by others, it could spell more trouble for abacavir. It is noteworthy that the DSMB did not unblind the whole study, meaning that whatever they saw among people with lower viral loads, they didn't see danger in letting the trial go forward.

Along with tenofovir (sold alone as Viread and in the fixed-dose combinations Truvada [with emtricitabine/FTC] and Atripla [Truvada + Sustiva]), abacavir is considered by most to be one of the most potent NRTIs. These negative study results are likely to raise more questions about when and how to use it.

A final note: during the 5202 session, the presenter mentioned, as an aside, that one person died in the study likely because they were put back on abacavir after an HSR, called re-challenge. With almost 10 years of experience using abacavir there's no reason this should happen, especially in an ACTG trial. Whatever the truth about abacavir and heart disease or high viral loads, there's no controversy over re-challenging. If a person has an HSR, or even a suspected HSR, they should never take abacavir again. While an initial HSR is unpleasant and often non-fatal, the reaction from a re-challenge with abacavir is drastically worse and is often fatal. It is crucial, even with HLA testing, that doctors and people with HIV be vigilant about abacavir HSR.

NEWS ON APPROVED ANTIRETROVIRALS

TRIO study's novel combination shows promise

by Paul Dalton

With well over 20 drugs from 6 classes available to treat HIV, there's growing interest in using novel drug combinations. Studies of class-sparing regimens are particularly important. While many new drugs have been developed over the past decade, the basic model of HAART — 2 NRTIs plus a potent drug from another class — has remained largely unchallenged. Results from a study presented at the International AIDS Conference may provide a boost for people seeking to investigate different ways of using HIV drugs.

The TRIO study is following around 100 people with extensive HIV treatment experience who were given a novel drug combination: the integrase inhibitor Isentress (raltegravir), the NNRTI Intelence (etravirine) and the protease inhibitor Prezista (darunavir). To enroll, people had to be on a failing drug regimen, with HIV levels above 1,000 copies/mL. All participants had extensive HIV drug resistance and limited treatment options. None had ever taken the drugs used in the study.

After 24 weeks, around 90% of people in the study had HIV levels below 50 copies. Of the 10 who had detectable HIV levels, only 3 had viral loads above 400 copies. On average their CD4 counts increased by 99 cells.

As good as these results are, there are two important caveats. First, there's no control group to draw comparisons to — which always weakens a study's observations. Second, these are early results from a planned 96-week study, so it's crucial to follow the study through to its conclusion.

Nonetheless these results hold promise. The drugs used in this study are among the newest developed. Most study to date of these drugs has been as part of traditional HAART regimens. This study suggests that at least these three HIV drugs (and possibly other) can be effectively combined in new ways.

A number of doctors have told Project Inform that they have been using this combination (sometimes called DUET-MRK after the DUET and BENCHMRK studies) in their clinics. While we support creative thinking and innovative approaches to HIV treatment, we also know that there's no substitute for solid scientific evaluation.

NEWS ON APPROVED ANTIRETROVIRALS

Mexican study may forecast advanced naíves

by Paul Dalton

Data from a study called the 'Mexican 5142 study' were presented August 5 at the International AIDS Conference. The study, a head-to-head study of Sustiva (efavirenz) vs. Kaletra (lopinavir + ritonavir) in people with CD4 counts below 200 who start first line HIV therapy, showed Sustiva to be more potent than Kaletra in this group.

This study enrolled 189 people in several centers around Mexico. Everyone had CD4 counts below 200/mL and had never taken HIV treatment. The presenter, Dr. Sierra Madero, pointed out that in Mexico, and throughout Latin America, this is a common situation for first line HIV therapy.

Participants were randomly chosen to take either the older, soft gel Kaletra or Sustiva, along with the fixed-dose combination Combivir (zidovudine/AZT + lamivudine/3TC). The primary endpoint of the study was the proportion of people with HIV levels below 50 copies/mL after 48 weeks. They also looked at changes in CD4 counts. A total of 85% of the participants were male, and the average CD4 count at the start of the study was 64 for the Kaletra group and 52 for Sustiva.

After 48 weeks, 70% of people on Sustiva had HIV levels below 50 copies, compared to 54% on Kaletra. Interestingly people taking Kaletra had slightly larger gains in CD4 counts: 167 cells vs. 157. More people stopped their treatment in the Kaletra group: 34% vs. 27%. There were also greater increases in total cholesterol (62 vs. 53 mg/DL) and triglycerides (62 vs. 167 mg/DL) in people taking Kaletra compared to Sustiva.

It's important to point out that the older, soft gel formulation of Kaletra was used in this study. Some studies have shown higher rates of gastrointestinal side effects in people using the soft gel, compared to the newer hard capsule version. This might explain part of the differences seen in discontinuations and treatment failures.

This study is of similar design to the ACTG 5142 study, which also compared Sustiva to Kaletra as first line treatment. The major difference is that the people in this study had lower average CD4 counts and more advanced disease.

This study is interesting for several reasons. First, while US treatment guidelines recommend starting treatment well before it was started in this study, a growing number of people, both worldwide and in the US, are being diagnosed with HIV with low CD4 counts. Information on treatment outcomes for this group is particularly important.

Second, for many years it was commonly believed that boosted protease inhibitors, like Kaletra, were more potent than NNRTIs. This study suggests this may not be true.

Lastly, this study confirms the finding from many other studies that boosted protease inhibitors tend to lead to larger increases in CD4 cells than NNRTIs.

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

NEWS ON APPROVED ANTIRETROVIRALS

Isentress gets another good grade

by Paul Dalton

Data were presented August 4 at the International AIDS Conference on a head-to-head study comparing the integrase inhibitor Isentress (raltegravir) to Sustiva (efavirenz) in people taking HIV drugs for the first time. The study found that Isentress proved equally potent and durable to Sustiva, the most widely used drug in first line treatment.

Marty Markowitz presented 96-week results from a phase II, dose-ranging study of Isentress. In the earlier phase of the study, volunteers were randomly assigned to take 1 of 4 doses of Isentress (100, 200, 400 or 800mg, twice daily) or Sustiva, each along with Truvada (tenofovir + emtricitabine). After 48 weeks, everyone taking Isentress was moved to the 400mg group, which was the dose chosen to move forward.

Earlier study data showed that Isentress performed equally to Sustiva. The results presented today showed that Isentress is comparable to Sustiva over almost 2 years of use. These results agree with preliminary data from a similar, but larger head-to-head study of Isentress vs. Sustiva.

After 96 weeks of treatment, 84% of people taking either Isentress or Sustiva had HIV levels below 400 copies/mL. Similar numbers were seen when looking at the percentage of people with HIV levels below 50 copies (83% for Isentress vs. 84 % for Sustiva). Both groups experienced an increase in CD4 cells of about 200.

The major difference was in the frequency of adverse events, with 51% of people taking Isentress reporting any adverse events, vs. 74% on Sustiva. Most of the difference was due to the neuro-psychiatric side effects associate with Sustiva. Isentress also had less of an effect on lipids than did Sustiva.

One audience member questioned why the 400mg dose was chosen over the others, given that earlier reports had shown little difference in overall reductions in HIV levels. Markowitz cautioned that he was not speaking on behalf of Merck, who makes Isentress, but reported that the dose was chosen based on 'extensive pharmacokinetic studies,' which found a high degree of variability in people taking Isentress. He mentioned that there was talk of studying Isentress as a once a day treatment, for people taking HIV drugs for the first time.

As mentioned earlier, this smaller study confirms what has been preliminarily reported from an ongoing larger study of Isentress vs. Sustiva in people taking first line therapy. There's intense interest in Isentress, which has shown some interesting, and possibly unique, characteristics. A quick look at *www.clinicaltirals.gov* — a central repository of clinical research — shows over 50 ongoing studies involving Isentress, from drug interaction studies to intensification and substitution studies.

While these results show that Isentress is comparable to Sustiva in people on first line therapy, it's unlikely to result in any significant changes in the way Isentress is used. For one thing, Isentress is only FDA approved for use by treatment experienced people, and this study will not change that. Also, as a panelist in an earlier talk pointed out, using either Isentress or Selzentry (maraviroc) — another new HIV treatment — would result in doubling the cost of treatment. With little data, and the increasingly tight budgets for programs like Medicare, Medicaid and ADAP, it is unlikely that many people will switch from cheaper, more studied first line options like Sustiva and Kaletra (lopinavir + ritonavir) any time soon.

Nonetheless, these results should be seen as more good news for Isentress, and for people living with HIV. The more drugs that are shown to be effective and well tolerated the better.

NEWS ON APPROVED ANTIRETROVIRALS

Heat stable formulation of Norvir appears likely

by Paul Dalton

In a late-breaker session at the International AIDS Conferenc, Abbott announced progress on their long-delayed heat stable form of their booster, Norvir (ritonavir). Now several years after their successful development of a heat stable form of Kaletra (lopinavir + ritonavir), this news is welcomed.

Norvir was originally developed as a protease inhibitor, but it fell out of use due to its high side effect rates and manufacturing problems. It continued to be used in low doses to boost the levels of other protease inhibitors. Its current formulation requires refrigeration. While this is an inconvenience for some, more importantly it is a major barrier to delivering boosted protease inhibitors to resource-poor areas of the world, where maintaining the necessary 'cold chain' isn't possible.

In 2005, Abbott gained approval for a heat stable formulation of Kaletra. They used a technology called Meltrex (*melt extrusion*) to reformulate Kaletra. Ever since people have been wondering when, and even if, Abbott would do the same for Norvir.

Earlier this year Project Inform learned Abbott had made significant strides in developing their Meltrex formulation of Norvir. The study presented in Mexico City showed that the Meltrex Norvir is bioequivalent to the older soft gel formulation. This means that the two formulations achieve nearly the same levels in the body. They also showed similar rates and severity of side effects. Because the soft gel formulation of Norvir is already FDA approved, Abbott only needs to prove bioequivalence and safety to gain FDA approval to market the new formulation.

Abbott announced plans to file with the FDA by the end of 2008. The FDA then has 6 months to issue a ruling, meaning this formulation is likely to be on pharmacy shelves towards mid-2009.

This is welcome albeit long overdue news. Many have openly questioned the reasons for the long delay between the Meltrex formulations of Kaletra and Norvir. Was Abbott trying to protect the market position of Kaletra, by keeping it as the only boosted PI that didn't require refrigeration? Abbott took pains to detail the missteps and formulation failures it encountered along the way, showing pictures of grossly swollen tablets for illustration.

It's noteworthy that other companies, including Pfizer and Gilead, are now developing their own boosters. Is the specter of impending competition the real motive? Maybe, but it will be some years before any new booster makes it to market. Whatever the back-story, a heat stable form of Norvir is indeed welcome news, particularly for expanding treatment into resource-poor areas.

NEWS ON EXPERIMENTAL ANTIRETROVIRALS

Researcher presents vexing information on rilpivirine

by Paul Dalton

In a presentation perhaps most notable for what wasn't said, data on Tibotec's experimental first line NNRTI, rilpivirine, were presented August 5 at the International AIDS Conference. The results showed that rilpivirine was equally potent and well tolerated as Sustiva (efavirenz) when taken as part of first line therapy. While the results presented were promising, the lack of forthrightness regarding questions on resistance and adverse events left many, including Project Inform, shaking their heads.

Developing rilpivirine as a first line NNRTI is welcomed by most in the scientific, activist and prescribing communities, since Sustiva has long been the only first line NNRTI option for many people. Sustiva's well known problems with sleep disturbances, depression and other neurologic and psychological adverse effects make it problematic, particularly those with pre-existing psychiatric issues — which accounts for a large segment of people living with HIV.

The data presented were from a head-to-head, phase IIb study of 3 doses of rilpivirine vs. Sustiva, both taken along with 2 NRTIs [either Combivir (zidovudine/AZT + lamivudine/3TC) or Truvada (tenofovir + emtricitabine/FTC)]. In total there were 368 volunteers in the study: 279 in the 3 rilpivirine groups and 89 in the Sustiva group.

Interestingly all 3 doses of rilpivirine proved as good as Sustiva at reducing HIV levels. After 96 weeks, 71–76% of people on rilpivirine had HIV levels below 50 copies/mL, compared to 71% taking Sustiva. All groups experienced similar increases in their CD4 counts: 146–172 for people taking rilpivirine vs. 160 for those on Sustiva.

Overall there were similar rates of adverse events reported: 12.2% for rilpivirine vs. 14.6% for Sustiva. However, this is where things got interesting. Despite overall similar rates of adverse events, only data on ones like rash, neurologic disturbances and increases in cholesterol and triglycerides that were more common for Sustiva were detailed. Moreover, when an audience member asked the presenter, Dr. Santoscoy, what adverse events were more common for people taking rilpivirine, no clear answer was given.

The story was similarly vexing in terms of the emergence of resistance. Comparable numbers of people experienced failure taking rilpivirine or Sustiva — around 6–7%. While the mutations, like K103N and Y181C, associated with failure on Sustiva are well known, little has been reported on which mutations confer resistance to rilpivirine. When asked by an audience member which mutations were seen on failure to rilpivirine, Dr. Santoscoy would only say that this study was too small to provide definitive answers to this question.

While it's true that this study is too small to provide definitive information on either resistance or adverse events, there's nothing preventing Tibotec from sharing what has been learned to date. It is fair to say that most in the audience were unhappy with the lack of direct answers. Until such time as Tibotec chooses to share detailed information on both adverse events and resistance, all we can say is that we don't know. Project Inform hopes that they don't wait long to provide the activist and scientific communities all the information we need to better understand rilpivirine.

While all 3 doses of rilpivirine reduced HIV levels equally, the higher doses were more likely to cause a change in heart rhythm called Q-T prolongation. The lower 25mg dose was chosen to move forward into larger studies. Martin Delaney, founder of Project Inform, wonders if 25mg worked as well as it did, and should an even lower dose be just as effective?

In the evening following this presentation, a member of Tibotec's research and development team responded to Project Inform's request for clarification on the outstanding issues regarding resistance and adverse events. Here is what we learned:

- The most common NNRTI associated mutation that emerged in people experiencing virologic failure on rilpivirine was 138K. Earlier laboratory work had found that this mutation had only a small affect on rilpivirine's potency. One person in this study had this mutation at the beginning of the study and remained undetectable at 48 weeks.

- More work will need to be done to see if 138K — which was recently added to the IAS list of NNRTI associated mutations — is indeed responsible for the virologic failures seen in this study.
- The one adverse event that was seen significantly more often in people taking rilpivirine was anemia. All the cases of anemia were seen in people taking AZT, and improved when they switched from AZT to tenofovir. It's interesting to note that people taking AZT with Sustiva had lower rates of anemia than either people on rilpivirine in this study or people taking AZT + Sustiva in other studies. It might be that there's a synergistic relationship between rilpivirine and AZT, leading to higher rates of anemia, or it could be from chance. Earlier research on shorter term use of rilpivirine, both in HIV-positive and -negative people did not show anemia.

It should be noted that this information came from a phone conversation between Project Inform and a representative from Tibotec. Project Inform has not yet seen actual data on either resistance or adverse events. When such data are made available, we will promptly report them.

NEWS ON EXPERIMENTAL ANTIRETROVIRALS

Apricitabine continues to show good results

by Paul Dalton

Data on the experimental NRTI, apricitabine, were presented August 5 at the International AIDS Conference, showing it is well tolerated when taken by people with experience taking HIV drugs. The results add to earlier research which showed that it might prove to be a good treatment option for people whose HIV has grown resistant to the NRTIs Epivir (lamivudine/3TC) and Emtriva (emtricitabine/FTC).

Dr. Cox, of Avexa (the company developing apricitabine), presented data comparing 2 doses, (600 and 800mg) taken twice daily to 150 mg of Epivir, in people failing an HIV regimen with Epivir.

After 24 weeks, no serious adverse events or deaths occurred in people taking apricitabine. Most were mild or moderate and were GI-related, including diarrhea and nausea. The overall rates of adverse events were similar between people taking apricitabine and Epivir. This is good news for Avexa as Epivir is widely considered one of the best tolerated HIV drugs.

While these safety data are encouraging, the bigger question facing apricitabine is how potent it is. Earlier presentations on this study suggested relatively good short-term anti-HIV activity, but longer-term data failed to show a statistically significant difference between people on apricitabine vs. those who continued on Epivir. At the 2008 CROI, people from Avexa claimed this might be due to the high potency of the optimized background therapy used by both groups in the study. While this might be true, Avexa still must prove that apricitabine is both potent and well tolerated.

NEWS ON EXPERIMENTAL ANTIRETROVIRALS

Two new NNRTIs enter the pipeline

by Paul Dalton

Data on two novel NNRTIs were presented at today's late-breaker session at the International AIDS Conference. After years with little development for this important class of HIV treatments, news on two somewhat promising compounds is welcome.

IDX899

IDX899 is being developed by Idenix, a small pharmaceutical company based in Cambridge, MA. Carlos Zala presented data from a small Phase I proof-of-concept study. A total of 30 people were given either a placebo or 1 of 3 doses (200, 400 or 800mg once daily) for seven days.

At the end of the study, people taking IDX899 experienced drops in their viral loads between 1.73 and 1.82 logs, while those taking placebo saw their viral loads rise slightly. The differences among the different doses were not significant.

Interestingly there was also not a strong relationship among the different doses given and the levels of drug measured in the body. When asked by an audience member to explain this, Dr. Zala had no clear explanation, but he pointed out that the levels were consistently far above those necessary to inhibit replication of HIV. This led the company to open another arm of the study, looking at a 100mg dose. No data on that group were presented.

There were few adverse events reported in the study, including no incidence of rash or neurological changes. However, the study was very small and short-term. More information will come out in larger studies being planned.

RDEA806

RDEA806 is an experimental NNRTI being developed by Ardea Biosciences of San Diego, CA. Graham Moyle presented data from a Phase IIb dose ranging study of 48 people who had never taken HIV drugs. People took either a placebo, 400 or 600mg twice a day, or 800 or 1000mg once a day for 7 days.

At the end of the study, people taking all of the doses of RDEA had lower HIV levels of between 1.7 and 2.0 logs, where people taking the placebo saw a small increase. Overall the drug was well tolerated with few adverse events reported.

One of the potential drawbacks for this drug is the relatively high doses being studied for once daily use. One audience member asked how it would compete with rilpivarine, another experimental NNRTI closer to possible approval. Moyle pointed out that rilpivarine had several hurdles to overcome and the company would evaluate the future of their drug in this light.

Commentary

The NNRTI class has long been dominated by Sustiva. It is good news to see several new drugs with promising properties, like good potency and tolerability. These two drugs are very early in development, so much more research will be done before we know whether either will be a good option for people with HIV. Nonetheless, with the pipeline as thin as it is, all good news on new HIV drugs is welcome.

NEWS ON OPPORTUNISTIC INFECTIONS

Interferon may lead to new option for treating TB

by Alan McCord

Worldwide, tuberculosis (TB) is the leading cause of death in people living with HIV. Indeed, simply having HIV is a major risk factor for developing TB. Treating it is difficult: therapy lasts 6 months, side effects interfere with treating HIV disease, and many do not complete their treatment.

Interferon gamma (IFN-g) is an important immune system chemical made by CD4 cells. It helps fight viral infections and prevent malignant cells from developing. As a medical product, IFN-g is well studied as a treatment for immune system diseases. Typical side effects include flu-like symptoms and injection site reactions.

Since CD4 cells can be depleted by HIV disease, insufficient amounts of IFN-g are present to protect the body from various infections. The Russian study looked at whether giving doses of IFN-g would improve immune responses to TB disease.

This small safety study followed 21 HIV-positive people with CD4 counts above 350. All were newly diagnosed with active TB disease of the lungs, and treatments were given to two groups. The first took standard TB drugs with 3 injections of IFN-g (500,000 IU) each week for 8 weeks. The second group took standard TB drugs and placebo injection. Lab tests were taken at weeks 0, 4 and 8.

Overall, results showed that those on IFN-g had better improvements in their general health and immune responses compared to placebo. IFN-g appeared to be well tolerated, though specific side effects were not reported. CD4 counts increased an average of 70–100 cells. HIV viral loads in the control group with IFN-g became undetectable in 11 people, while no one became undetectable in the placebo group.

Taking drugs for both TB and HIV at the same time can be challenging for many. As well, the risk for developing TB within the first 3 months on HIV therapy is quite high. Therefore, using IFN-g in people who haven't started HIV therapy may eventually provide another option for those faced with a TB diagnosis. Longer-term studies will need to be conducted to assess how durable this response remains over time.

NEWS ON OPPORTUNISTIC INFECTIONS

High HPV rate calls for new screening protocols

by Alan McCord

A growing area of concern in the health of people living with HIV is the role that the human papillomavirus (HPV) plays in causing cervical and anal cancers. Expanding research over the past two years has helped bring this concern closer to the forefront of the community's attention. Research is showing higher rates of HPV infection and disease in HIV-positive people than originally believed.

HPV is easily passed through sex, and about 130 types have been discovered. Most do not cause symptoms, while nearly 40 low-risk types can cause genital warts and another dozen or so high-risk types can cause cancer. People living with HIV are at higher risk for getting HPV infection and disease.

A Venezuelan study presented at the International AIDS Conference investigated the rate of high-risk HPV and high-grade *anal intraepithelial neoplasia* (AIN) in HIV-positive men who have sex with men (MSM). AIN is abnormal cells found in surface anal tissue. It is not cancer, but it can lead to other health consequences, including cancerous cells, invasive anal cancer and surgery.

AIN is more common in MSM than other populations, as is anal cancer. This is likely due to a higher rate of anal sex in this population. However, anal HPV and AIN can still develop in any man or woman with HIV, even if they haven't engaged in anal sex. In fact, one study found higher rates of anal HPV in women than in men.

The study followed 188 men. Blood tests provided CD4 counts and viral loads along with low-risk types (6, 11) and high-risk types of HPV (16/18/31/33/35). Average age was 40, average CD4 count was 354, and average viral load was 3.21 +/- 16 log copies HIV RNA.

Each volunteer also had an anal exam, which included the swabbing and collecting of surface anal tissue and mucous. If the exam uncovered an abnormal condition, then a biopsy (surgical removal of tissue) was performed. All samples were evaluated for low-grade and high-grade AIN.

HPV was found in 56% of the volunteers, though it was found in 75% of those with lesions in surface anal tissue. About 42% of the volunteers showed high-grade AIN, another 42% were normal, and only 0.5% showed low-grade AIN.

Both high- and low-risk HPV were detected in the samples. Nearly every volunteer had some type of anal HPV and often had more than one. High-grade AIN was also identified in the presence of high-risk HPV. The high rate of AIN found in this population may eventually lead to high rates of other cancerous conditions.

Studies like this one demonstrate the need for standards of care for screening and treatment. The growing rate of HPV disease in people living with HIV needs assertive attention by medical providers to proactively identify these possible health risks. These results will help contribute to creating standards of care that are not yet in place to properly address these conditions.

NEWS ON OPPORTUNISTIC INFECTIONS

Studies further identify risks for TB while on HAART

by Alan McCord

Globally, diagnosing and treating tuberculosis (TB) in people living with HIV is becoming more difficult, as multi-drug resistant and extensively resistant strains become more common. This difficulty is often worsened by the lack of testing resources, access to drugs, and health care infrastructures. In spite of these complex issues, it's becoming more imperative to properly screen and treat individuals at risk for TB disease. Several studies on TB/HIV co-infection reported results at the International AIDS Conference.

Risk factors for TB within first 3 months on HAART

This retrospective study examined data from 12 cohorts of 9,937 HIV-positive people in North America. Researchers compared the risk of TB within and after the first 3 months on HAART. No one who had TB before or in the same month of starting HIV therapy (HAART) was included. However, those with earlier AIDS-defining conditions, except TB, were included.

Four cases of TB were found within the first 3 months on HAART, while 38 cases of TB were found afterwards. The risk factors found for the 4 were low CD4 counts (below 100 cells) and high viral loads (above 250,000). No differences were seen by age, sex, race, place of disease (inside vs. outside lungs), TB status (positive vs. negative), and type of HAART that was used.

These results show the need for health providers to thoroughly screen (and treat as needed) people who have low CD4 counts and high viral loads when starting HIV therapy. These are not radically new suggestions for assertive screening and treatment of opportunistic infections (OIs), as many OIs occur at these levels. What's clearer is that the risk for TB disease in these individuals is more pronounced before and within the first three months on HAART.

When to start HAART after a TB diagnosis

The best time to start HAART after a diagnosis of TB remains somewhat unclear. The Brazilian THRio study examined a large group of individuals for length of survival after a TB diagnosis. It compared the impact of HAART over time as well as its timing on survival.

This retrospective study examined the records of more than 15,000 people with HIV. The study identified three groups for comparison: starting vs. not starting HAART after a TB diagnosis; starting HAART during vs. after TB treatment; and starting HAART within 60 days, 61–180 days, and over180 days of a TB diagnosis. Men comprised 66% and women 34% of the study.

A total of 660 were diagnosed with TB and 461 of them had started HAART. Those who started HAART after a TB diagnosis had a significantly lower risk of death than those who didn't start HAART. Those who completed their full treatment for TB were also less likely to die and had better outcomes than even those on HAART alone. However, the results showed that timing the start of HAART had no significant effect on survival, nor did the three ranges of time studied.

These results are not surprising, as it has often been shown that taking HAART as prescribed improves health outcomes and helps resolve opportunistic infections (OIs) such as TB. This would also include completing any therapy for an OI such as TB. Interestingly, however, these study results contrast with another study's results (directly below) that show starting HAART sooner after a TB diagnosis lowers the rate of death.

Starting HAART and its impact on survival

A small retrospective study from Iran examined 69 people with both HIV and TB over 5 years. Two groups were compared. The first had CD4 counts below 200 and started HAART after 8 weeks on TB therapy. The other group started HAART either 2 weeks after starting TB therapy (if CD4 counts were below 100) or 8 weeks after starting TB therapy (if CD4 counts were 101–200 cells). The study looked at the response to TB therapy, liver function and the development of IRIS (immune reconstitution inflammatory syndrome) or new OI.

Results showed that the two groups were comparable in terms of drug reactions and the development of IRIS or a new OI. However, the second group — who in general started HAART earlier after taking TB therapy — showed fewer deaths. These data conflict with results found in the study directly above, though this may or may not be significant. Because this was a smaller study, the fewer deaths may not represent a conclusion that could be made to a larger population.

Final thoughts

Worldwide, 2 billion people are infected with TB, while 9.2 million new cases of TB disease occur and 2 million die each year. Resource-poor areas of the world find it difficult and often impossible to adequately detect and treat those living with both HIV and TB. The newer, harder-to-treat strains of TB further complicate medical decisions.

From the studies mentioned above and others, two lab markers are associated with higher risk for TB disease. These are high viral load of 250,000–350,000 or more and low CD4 cell counts below 100. In these individuals with advanced HIV disease, it's wise to aggressively screen for TB infection and disease just before and within the first 3 months of starting HAART.

It's clear from many studies that being on HAART helps resolve TB infection and disease, provided that the treatments for both are taken as prescribed. However, the best time to start both (such as 2 weeks or 8 weeks apart, for example) is still not clear. These results do point to more aggressive screening of those at risk for TB right before and after starting HAART. These tools include not only PPD skin tests, anergy tests and chest x-rays, but also and perhaps more importantly sputum samples and cultures that show actual bacteria.

NEWS ON HIV RELATED CONDITIONS

Anti-depressants not linked to increasing risk of cancer

by Alan McCord

Some studies have suggested a possible link between using some types of anti-depressant medications to a heightened risk of cancer. There is also evidence that certain anti-depressants might lower the risk of some cancers. Understanding the possible link between anti-depressants and cancer is particularly important for people wit HIV, because they experience higher rates of cancer than the general population, and they have a high rate of anti-depressant use.

In an abstract presented at the International AIDS Conference, antidepressants were found to not increase this risk. This large study followed 10,997 individuals at an HIV center both before and during the era of highly active antiretroviral therapy (HAART). A total of 2,004 were prescribed anti-depressants while 1,607 individuals were diagnosed with cancer during the time covered by this study. It examined the changes in the incidence of cancers based on how long they were taking antidepressants.

An analysis established the risk of both AIDS and non-AIDS cancers. This was done for each class of anti-depressants: SSRIs (selective serotonin reuptake inhibitors), TCAs (tricyclic antidepressants), and other drugs for depression. The study examined data from the time that the individuals were exposed to antidepressants, before and during the era of HAART.

The results showed that there were no significant connections between any class of anti-depressant and any type of cancer, which included SSRIs not altering the risk of Burkitt's lymphoma. This held true for individuals both before and during HAART. Thankfully, due to the number of scripts that are currently written, anti-depressants do not affect cancer risk in people living with HIV.

NEWS ON COMPLEMENTARY THERAPIES

Milk thistle may help improve liver health in people with HIV and hepatitis C

by Alan McCord

Those co-infected with HIV and hepatitis C (HCV) can face significant challenges with sustaining their liver health. This is due to how the two viruses affect the liver over time as well as the ongoing side effects from taking drugs that treat the two diseases. For these and other reasons, there's an urgent need to find methods of improving liver function for people co-infected with HIV/HCV.

A report from a small study of the popular herbal supplement, milk thistle, was presented at the 2008 International AIDS Conference. The study looked at its ability to improve liver function in co-infected people. Milk thistle, or *silybum marianum*, has been shown in other studies to benefit liver function in various situations, though many of those studies were not well designed or came to inconsistent conclusions. This study used an extract from the milk thistle seed called *silymarin*.

This 52-week study of 21 co-infected volunteers examined how safely milk thistle performed. They were randomly assigned to take either a placebo or 180mg of 80% standardized silymarin extract 3 times a day. Out of the 21 who started, 15 finished the study with 7 who were on silymarin and 8 who took placebo. In both groups, volunteers were about equally men and women and were mainly African American and Latino.

The results showed no impact on CD4 counts or HIV or HCV viral loads. There were no serious adverse effects, although the abstract for this study lacked details on what adverse effects were seen. Since HIV viral load was not affected, this suggests that milk thistle may not interact with HIV or HCV drugs, although there was no information on HIV regimens used by study participants.

The most notable result was a trend in lowering the *aspartate aminotransferase* (AST) levels in those who took milk thistle. (AST is a blood marker that indicates tissue damage in the liver.) There was a decline in AST of 8.4 for those on milk thistle, while the placebo group showed an increase of 27.9 in their ASTs.

Although this looks like good news, people should be careful not to run out and pick up over-the-counter milk thistle products for this use. The study used an extract of milk thistle, which may or may not be found in retail products. These products also often contain other ingredients that can alter their effectiveness. Additionally, since this was a small safety study, not enough data is known about how milk thistle interacts with the various HIV and HCV regimens available today. The degree of improved liver function and how long it may last also need to be furthered studied.

NEWS ON IMMUNE BASED RESEARCH

IL-2 study results may offer unique solution

by Alan McCord

Results from a study of IL-2 (interleukin-2) garnered substantial interest from a full audience August 6 at the International AIDS Conference. Though IL-2 is the most studied immune based

therapy, its usefulness as an adjunct for HIV therapy mostly hasn't panned out, except as an experimental drug for discreet use in a select group of people. However, these results are quite exceptional and have the potential to offer a person to take extra time before starting HIV therapy.

IL-2 works with the immune system to create a stronger defense against HIV infection. In general, the theory has been to activate the immune system to produce more immune cells in order to combat and control HIV. (Some inaccurately refer to this as "boosting".) However, this hasn't worked because the activation actually causes unwanted and sometimes life-threatening side effects.

What's intriguing about how IL-2 was used in this study is that the researchers used it before a person went on HIV therapy, unlike how much of IL-2/HIV research has so far done. The theory here was to prevent the loss or improve the level of CD4 cells and thus defer the start of HIV therapy. Since the current Federal Guidelines recommend starting therapy at or below 350 CD4s, keeping them above that mark was the goal for the study.

The study enrolled 130 people with HIV and randomly assigned them to two groups: those on IL-2 (66) and those on placebo (64). All had CD4 counts from 300–500 (average 383) and had average viral loads of 4.36 log10 cp/ml. None had signs of HIV progression. Those on IL-2 received 4 cycles twice a day for 5 days, every 8 weeks for the first 52 weeks. After that, 2 optional cycles per year were offered but not required.

In this study, those volunteers who experienced any one of 4 different events by week 96 were taken off IL-2 therapy and started on HIV therapy. These events were: a CD4 count below 300, an independent decision to start HIV therapy, the diagnosis of an AIDS-defining condition, or death. The study extended its follow-up on the volunteers to 150 weeks.

The results are quite remarkable. Through week 96, the average change in CD4 counts was +51 for the IL-2 group and -64 for placebo. There was no difference between the groups in terms of vial loads. This is an important finding, as one of the fears of IL-2 therapy is that it might cause HIV levels to rise. For those on IL-2, CD4 count and viral load changes predicted HIV disease progression; while for those on placebo, only their CD4 count change predicted progression.

Even more remarkable was that for volunteers with lower viral loads (below 4.5 log10 cp/ml) at the start of the study, the likelihood that their HIV did not progress was 66% for those on IL-2 and only 10% for those on placebo. This allowed those IL-2 volunteers to delay starting HIV therapy by up to 92 weeks on average! These results are striking given the amount of time without therapy and the similar rate of adverse events between the two groups.

It should be noted here that this study used a lower dose of IL-2 than has been used in other studies, like SILCAT and ESPRIT. Still, people taking IL-2 reported feeling fatigue, fevers and other 'flu-like' symptoms while on IL-2 therapy. While the severity of these symptoms may have been less due to the lower dose used in the study, these side effects are a major drawback for IL-2.

Once a person starts his or her HIV therapy, it's a lifelong commitment. Longer time off treatment might improve one's quality of life and offset long-term side effects seen with HIV therapy. If IL-2 can fill that void, then it's a step forward for those who can access the treatment. However, much more research will need to be conducted.

NEWS ON IMMUNE BASED RESEARCH

Immune based therapy offers intriguing possibility

by Paul Dalton

In part of a small but interesting session focused on immune based therapies, Dr. R. Gandhi of Massachusetts General Hospital presented data comparing two immune based approaches in people interrupting HIV treatment. The study compared injections of dendritic cells (DCs) alone vs. DCs + canarypox (CP) virus in people with undetectable HIV levels while on potent HIV treatment but undergoing a treatment interruption.

Volunteers had special blood cells called monocytes taken from their bodies, which were then treated with a cocktail of chemicals to turn them into DCs. These DCs are a type of antigen presenting cell that plays a key role in the immune response to HIV. The theory was that by adding a CP virus, which in some studies increases the activity of DCs, volunteers might better be able to control HIV replication when interrupting treatment.

In this randomized study, 29 people were assigned to get injections of DCs alone or DCs + CP virus 3 times, over a 15-week period. During their first 2 injections, everyone also received injections of a substance called KLH, to help measure the strength of the immune response. After the last injection everyone stopped their HIV treatment.

Researchers looked for differences in HIV levels after 10–13 weeks off HIV treatment. While overall there were no differences in HIV levels between the two groups, there were some hints that this approach might warrant more study.

Specifically, 4 people in the DC + CP virus group had HIV levels below 5,000 copies/mL after 10–13 weeks, compared to none in the DC only group. However, these differences were not sustained after one year. This short-term difference was intriguing enough to make the investigators consider more research on this approach.

It should be noted that this was a small study, the results which may pan out in larger study. It was also done between 4 and 5 years ago, before the most recent rash of negative studies on treatment interruptions, including SMART. Audience members and Dr. Gandhi discussed the ethics of this kind of study in light of the negative findings from SMART and similar studies.

COMMENTARY ON NATIONAL AIDS POLICIES

CDC unveils higher rate of annual HIV infections

by Alan McCord and Paul Dalton

New data released by the Centers for Disease Control and Prevention (CDC) show a substantially higher HIV infection rate occurring each year in the US. The announcement, through a special HIV issue of the *Journal of the American Medical Association*, coincided with the start of the 2008 International AIDS Conference.

According to the CDC, the new estimate for new HIV infections in 2006 is 56,300 — 40% higher than the previous estimate of 40,000. This resulted from the CDC's development of new methodology that they claim more accurately calculates the yearly estimate. This is due to better identifigying recent and longstanding infections, as well as improved mathematical modeling.

Although the 40% increase represents a substantially higher number over previous years, the CDC claims that the new figure does not represent an actual increase in new infections. The CDC states that the annual infection rate has remained fairly steady over the past decade, though underreported due to a lack of accurate statistical methodologies.

The report went on to state that men who have sex with men (MSM) and African Americans continue to bear the burden of new infections. Just over half of new infections occur in MSM, while African Americans account for 45% of new infections though they comprise 13% of the population.

In an interview, CDC's Kevin Fenton took pains to argue that this is simply a matter of new counting methods, not a real increase in infections. When asked what could be done to stem the stubbornly high rates of new infections, Fenton repeated the mantra of 'fewer sexual partners, abstinence and expanded testing.'

The lack of innovative thinking by the CDC in the face of these new numbers — which show a larger number of HIV infections however you frame it — is disappointing to say the least. Even if one accepts that this recalculation doesn't represent an actual increase in infections, it shows that current prevention programs are highly inadequate.

Adding to the story is the long delay between first reports of these numbers and the CDC making them public. Project Inform first heard that the numbers were being revised up to months ago, yet the information was withheld until the 2008 International AIDS Conference.

These figures are yet another wake-up call for community activists and the federal government to plan and implement a national strategy to effectively end the transmission of HIV in the US. Project Inform continues to work in coalition with organizations and individuals from the community, government and industry to implement the National AIDS Strategy. We also continue to provide leadership around exploring the value of interventions such as PrEP and microbicides.

COMMENTARY ON CURED BASED RESEARCH

The vaccine research community rebuilds its agenda

by Alan McCord

At the August 4 session, *Vaccines and Microbicides: Where Do We Go from Here?*, several panelists expressed their dogged resolve to continue HIV vaccine research. This comes after a mixed bag of advances and setbacks in prevention. On the positive side, male circumcision is now shown to prevent transmission. On the negative, most of the microbicides in study have failed and two major vaccine studies were recently cancelled.

After these recent setbacks, it was somewhat surprising that the message from the panel was a united front of optimism and due-diligence in finding a vaccine — or even several — that will ultimately prevent HIV infection. Though the message was littered with the word *failure*, the panelists spun it with tenacity ... in order to get beyond this blip in vaccine research, learn from those failures, and steadfastly plan and manage a truly effective global agenda.

The panel referred often enough to the integration of a more vigorous research agenda, the influential knowledge that comes from research "failures", and the implementation of short-, medium- and long-term strategies. These are not new concepts, but the message is now being delivered with

the tenor of an army of activists. However, if it is to work, then their task now is not only to follow through with the science but also communicate to and educate the public — not to mention an increasingly skeptical group of scientists and policymakers — on what's needed for the agenda to succeed.

Science is rarely a straight line. Indeed, most research relies heavily on what is learned from failures along the road to success. "Making new vaccines is one of the most difficult of human endeavors," stated Tachi Yamada, the new executive director of the Gates Foundation. "Only one in ten candidates succeeds." Yet, each of those failures informs the next stages of research. The panelists shared how researchers have hunkered down and strategically digested their learned lessons.

How have these failures influenced the outlook for a feasible vaccine? Many panelists acknowledged that we have to learn a great deal more about the fundamental basis of the human immune response. One of the fundamental obstacles to developing an effective vaccine against HIV is that nobody knows what kind of immune response, if any, is necessary and sufficient to block HIV infection — or as scientists call it the *correlates of immunity*. Then, with that, only look at the best candidates for success since not every product can be studied. A telling comment came midway through the session: "We need to move away from our home run mentality."

Innovation was mentioned often ... in collecting unique vaccine ideas, in attracting and retaining bright young researchers to the field, and in converging massive venture capital with new scientific ideas. (Most Nobel science laureates received their prizes for work they started before they turned 35.) Industry must also scale up its involvement, since pharma and biotech companies currently contribute only 10% of the total investment in preventive vaccine research. Together, all of these have the potential to broaden the global vaccine agenda and fashion a true cure for HIV.

More specifically, the panelists detailed several ideas. Produce invigorated preparations for studies, all the way back to the initial pharmacokinetics, study designs and toxicity acceptance levels. Perhaps reduce rather than increase the immune response. Promote more rather than fewer mutations. Focus research on those unique situations found in HIV, such as on long-term non-progressors.

The panel also clearly stated that educating the public must be a distinct component for engaging a successful agenda. This includes building effective affiliations with media. All told, there's a clear need for enormous resources, including a vast network of partners and ideas. As Susan Buchbinder remarked, "We cannot underestimate the value of our volunteers and the community."

The past few years have seen a series of setbacks for both vaccine and microbicide development. These have led to a good deal of soul-searching within the scientific, activist and even funding communities. The recent decision to cancel the PAVE 100 study, and instead look toward smaller proof-of-concept studies, reflects both the realization that the current approaches to vaccines have little chance at success, along with the need to move the science forward.

Should this renewed hope actually work, only time will tell. The coming year will be one of hope and scrutiny for the global vaccine agenda. Many look to the vast expertise that's available in the scientific world to produce a viable vaccine, yet in the same breath may wait to exhale for signs that this rehabilitated call to action will work.

NEWS ON CURE BASED RESEARCH

Elite controllers may show way to a cure

by Alan McCord

In light of the recent cancellation of two major vaccine studies, unique ideas are desperately needed to resolve the global AIDS crisis. The answer to this scientific riddle may lie in a group of people who naturally control HIV infection on their own, without help from HIV therapy. These *elite controllers*, or *long-term non-progressors* (LTNPs), represent less than 1% of all people with HIV.

Science has not studied LTNPs all that much compared to other areas of HIV research. However, more intense research is starting to be implemented. The August 11 session at the International AIDS Conference, *Elite Controllers and Long-Term Non Progressors*, presented results from several studies that may help explain why LTNPs resist HIV disease progression.

Study of the effects of IL-15

An Italian study sought to examine if the immune chemical IL-15 has an effect on HIV replication. Researchers collected blood samples from 13 LTNPs, 9 with HIV disease never on therapy, and 9 HIV-negative people. They used the chemical, *interferon gamma* (IFN-g), to stimulate IL-15 and compare the three groups both before and after using IFN-g.

The results showed that LTNPs have a significantly higher percentage of IL-15 than progressors, both in the walls of and inside immune cells. After using IFN-g, IL-15 levels significantly increased in LTNPs while it was nearly absent in progressors. In the HIV-negative samples, their capacity to respond to IFN-g was present, though not significantly. These results support the role of highly active and functional CD8 cells in LTNPs, which may be more able to use IL-15 as an immune therapy.

Study of the immune response of CD8 cells

A Spanish study followed 10 LTNPs over 4 years. The LTNPs were HIV-positive for more than 10 years, had more than 500 CD4 cells, and had never been on HIV therapy. The researchers examined the effects of 2 HIV proteins, *Gag* and *Nef*, on the type of immune response by CD8 cells. They studied 3 chemicals (MIP, TNF, IL2) produced by CD8s.

Over the 4 years, average CD4 counts and viral loads remained stable. The results showed that the 3 chemicals were produced in different amounts at different times. Overall, there was an increase from 10 to 50% of the 3 chemicals in response to the Gag protein. However, the CD8 response to Nef showed a decrease from 40 to 20%.

This suggests that an LTNP's immune response may evolve over time and may function in different ways in order to control HIV infection. Though this response has been noticed in other studies, there's little information about how stable it is over time. This study helps contribute more information to understanding this response, and may help lead to an immune therapy for HIV infection.

Study of how a person's genes react to HIV

Another Spanish study used new technology to examine how certain immune genes behave during HIV infection. The study included 16 LTNPs (HIV-positive for more than 15 years with no HIV therapy) and compared them to 17 others with more typical HIV disease: positive for less than 5 years, a loss of more than 50 CD4 cells each year, also with no HIV therapy.

The study showed 146 genes in LTNPs were active while 315 were active in the comparison group. The active genes in LTNPs were mainly involved at the cells' walls and in how they communicated with each other. In contrast, the genes in the non-LTNP group were mainly involved inside the cells with their cell regulation and division.

This difference may point to why LTNPs are successful in controlling their HIV infection, perhaps due to focusing more on cell signals rather than cell regulation and division. This finding will need to be confirmed in larger studies, but could help deepen our understanding of the immunologic differences between LTNPs and others living with HIV.

Study of telomeres and shelterin genes

Another US study looked at the roles that telomeres and shelterin genes have in HIV infection. A telomere is a gene that "caps" and protects the end of a human chromosome. (In Greek, *telo* = end and *mere* = part.) Shelterin genes are a group of proteins that protects telomeres. Together they help chromosomes maintain all their information when cells divide.

This study took blood samples from LTNPs (viral loads below 50, not on HIV therapy) and from progressors (viral loads above 30,000). It looked at 5 telomeres and 6 shelterin genes as they related to the control of HIV infection by CD8 cells. The results showed certain telomeres and shelterin genes have some relation to CD8 cells being able to function and control HIV infection. This information may be able to help identify new targets for gene therapy of CD8 cells.

Commentary

These fascinating studies and others like them are just beginning to unwrap some of the various genetic reasons how LTNPs may control their HIV infection. Though this field of investigation is truly in its infancy, it could some day yield information to help design gene, immune or other therapy that would eliminate the need for HIV therapy.

In each case, a great deal more study needs to be done. Most studies were done in the lab from blood samples, so the results may be quite different than when studied in animals or humans. However, taken collectively, these results show great promise into further understanding the intricacies of our immune systems, and may result in contributing to the eventual cure for HIV disease.

COMMENTARY ON BIO-MEDICAL PREVENTION RESEARCH

A cause for optimism: Microbicides pipeline shows promise

by Alan McCord

At the August 4 session, *Vaccines and Microbicides: Where Do We Go from Here?*, Zeda Rosenberg updated the state of research into microbicides. Her presentation spoke of renewed hope that the current pipeline of experimental drugs could, in a year or two, result in strong candidates for protecting women against HIV infection. This tone was in marked contrast to the general sense of disappointment that has permeated this important field for the past few years.

Microbicides are substances designed to prevent HIV and other sexually transmitted infections (STIs). They come in various products, such as gels, rings, films, tablets and capsules. As a woman-controlled method of contraception and STI prevention, the current candidates are vaginal products. Rectal application studies are being considered, though these are still in their infancy.

Microbicides offer women more control over their health. Other benefits include a low systemic exposure to the drug since it's not taken by mouth, fewer possible side effects, and less chance for resistance. Though the potential for these products is real, it's clear that one microbicidal strategy will not satisfy all women. Some may also need or want to use more than one product.

Her presentation started by acknowledging the setbacks over recent years in microbicide research. No less than 10 studies were stopped due to lack of effectiveness and safety issues. However, two studies are still ongoing: BufferGel and PRO 2000.

The bulk of her presentation focused on the next generation of products, many of which are antiretrovirals (ARVs). ARVs are potent and effective drugs used to inhibit and control viruses, including HIV. Many have already been developed for other uses, resulting in a good deal of accumulated safety and efficacy information.

Among the candidates furthest along in study is topical tenofovir. It's a widely used HIV treatment, sold by itself as Viread and as part of the fixed-dose combination pills, Truvada and Atripla. Eight safety studies have finished, and the next phase is being planned. Of all the microbicide candidates, this drug has the most advanced research backing its use, especially against HIV.

The highly potent NNRTI, dapirivine, is also being tested. Originally developed as a pill to treat HIV, this drug has been studied in a dozen different studies. Several dosage forms are in development, and a Phase 3 study is planned for 2010. The efficacy studies show a good level of drug release.

Two other NNRTIs are in study: UC781 and PC815. UC781 appears to be highly potent from 4 Phase 1 studies. Two more are being planned, as well as two Phase 1 studies in men. PC815 appears to be potent, though prevention studies are ongoing in primates. Phase 1 studies are planned for 2009.

Another HIV drug, the CCR5 antagonist maraviroc, is being studied as a topical gel. It's already well studied in treating HIV, and early assessment of its effectiveness as a microbicide is ongoing.

Aside from these, another nine candidates stand in the pipeline. These include BMS794, m167, RANTES analogs, L755 peptide and pyrimidinediones, among others.

Project Inform is encouraged by this level of current research and hopes that solid candidates will come forth in the near future. It's clear from a global perspective that these products can mean life or death for millions of women. In the US, the CDC's recent announcement that new infections in the US are 40% higher than previously thought shows the dire need for new prevention efforts domestically. Although these vaginally dosed products are a welcomed addition to HIV prevention, microbicides must also be developed in rectal use, for those who engage in anal sex.

Project Inform continues to support, advocate and provide leadership around biomedical prevention that further reduces the number of new infections, like microbicides. Included in this is our leadership role within the newly formed PrEP (Pre Exposure Prophylaxis) Working Group, founded by CHAMP.

COMMENTARY ON BIO-MEDICAL PREVENTION RESEARCH

HIV sexual transmission under HAART: Project Inform comments on 2008 Swiss Statement

by Paul Dalton and Alan McCord

In January 2008, the Swiss AIDS Commission issued a controversial Statement on the transmission of HIV in heterosexual mixed status couples. It stated that HIV is not likely to be passed on when the positive partner fully adhered to a potent HIV regimen, had undetectable viral load for at least six months, and did not have any other sexually transmitted infection (STI) during that time, even despite sex without condoms.

What ensued has been tumultuous community discourse and opinion pieces worldwide. Some have denounced the Swiss Government as irresponsible. Others responded with "no comment". Few others, like Project Inform, invited this as a way to discuss issues faced by people living with and affected by HIV.

This outcry stems from the perception that the Swiss Government was saying that people who take effective HIV drugs can stop having safer sex or abandon their condom use without infecting their partners. The panelists were clear: this is not their message. Some have criticized other aspects of the Statement, arguing it failed to address other issues, such men who have sex with men.

The Sunday afternoon session, *HIV Transmission under ART*, provided a forum to discuss this Statement. Seven panelists attempted to clarify the persistent questions that have lingered ever since to a crowd of about 300. Project Inform believes the conversations the Statement has spurred can help inform discussions formany people living with HIV, as detailed below.

For Project Inform's response to the Statement by the Swiss AIDS Commission, go online to *www.projectinform.org/advo/pp/swiss.shtml*.

Understand this statement in its context.

At various points throughout this epidemic, many medical, social and behavioral issues have emerged. We have grappled with the risks of casual transmission and oral sex — each without definitive research. In these cases, observations and an understanding of the mechanics of HIV transmission helped mold recommendations that have stood the test of time. A study called HPTN 052 is currently enrolling, designed to answer the risks of transmission under HAART. The results likely won't be available until 2016, at which point we may look back and wonder what the commotion was all about. We also might ask ourselves, how many new infections could have been prevented in the meantime?

Understand the limitations of the statement.

Too often critics of the Swiss Statement have used its limitations to dismiss the it entirely. This is both scientifically and ethically unsound. Science works best when studies and reports are examined honestly, taking into account both their strengths and weaknesses. Some have said it's premature to talk about these data until such time that there are more mature and definitive results. One panelist reminded the audience of the experience of male circumcision where 17 years elapsed between the emergence of supportive circumstantial evidence in reducing HIV infection rates, and the definitive results from prospective, randomized studies.

It is possible to encourage conversations with couples on issues that they can do something about. This includes encouraging each partner to disclose his/her status, to discuss their fears, or to even start engaging in safer sex, among many others. In some parts of the world, health care

systems are overburdened and cannot accommodate these discussions. For many, viral load or STI tests are unavailable. For others, medical infrastructures barely exist. Though the world has reacted to this Statement, it may very well not apply to most of the planet.

A weakness of the Statement is that the data came from studies of heterosexual sex. In the US, the CDC estimates about half of new HIV infections are among MSM, reinforcing the importance of studying the impact of treatment on prevention among this group.

Provide accurate information.

The Statement provides a good deal of applicable data, much buried beneath the vocal backlash. Physicians, community workers and others who interact with HIV-positive people and their partners can and must provide information clearly and accurately. The basic model of fully informed decision-making that has defined Project Inform's approach to HIV treatment decisions is just as applicable to this situation.

Get regular health care.

One undeniable take-home message is the critical importance of having accurate medical information to make informed decisions. Vast inequalities in access to things like viral load tests and STI screening must be accounted for in settings worldwide. Some panelists felt that these differences render the Statement largely meaningless to most people with HIV. Project Inform sees it differently. It is much like the early data on combination therapy: information that might have only applied to few people at that time can have profound implications for far more people down the line. As seasoned AIDS activist Heidi Nass puts it, 'progress in progress.'

Use this as a tool.

Project Inform encourages sophisticated conversations among mixed status couples and others. After nearly three decades of the epidemic, a great deal is known about how HIV is and is not passed. Each partner, along with their doctors, can be encouraged to discuss these issues. These data, when discussed alongside a person's needs for true sexual intimacy, can lead to fuller and more honest discussions between sexual partners.

As we have stated in our March 2008 response to the Swiss Statement, we encourage all sexually active individuals to learn their status by regularly testing for HIV; we encourage treating HIV as early as individuals are ready to start and the medical information suggests; we encourage adhering to HIV treatment while practicing safer sex; and we encourage the honest conversations between partners and their providers on the medical and behavioral issues of transmission.

Practice safer sex.

The Swiss Statement does not suggest individuals abandon using condoms or other safer sex practices. In fact, it spotlights the necessity for a couple's continued diligence in this area. One panelist argued that condom use without treatment is about as protective as treatment without condoms. The Statement argues that the best possible prevention comes from combining treatment and condoms. Accurate information on transmission risk should drive these decisions.

Also worth pointing out is how little attention has been paid to issues of pleasure, intimacy and stigma facing people with HIV throughout these public debates. While researchers might not place much emphasis on these issues, they're of great importance to people living with HIV. They have profound implications for their emotional and sexual well being.

Push this discussion to test for HIV.

The Statement underscores the need to reach those who are undiagnosed or untested. These discussions can only work when people know their HIV status. Most estimates show about 1 in 4 Americans with HIV do not know they have HIV. Project Inform encourages testing as a way to take control of one's life.

Explore ways to prevent HIV.

The Statement highlights the role that effective treatment plays in preventing new infections. Project Inform recently revised its mission statement to include biomedical prevention to help reduce new infections. This includes interventions such as Pre-Exposure Prophylaxis (PrEP), vaginal and rectal microbicides, and male circumcision, among others. These alternate methods should be considered as being additive and synergistic to behavioral interventions such as condom use. Therefore, no one method should preclude the others. The more choices one has, the better. The better the data are, the more confidence people can have in their choices.

The "asymmetry of risk".

One interesting point raised by a panelist was the *asymmetry of risk*. If you say something is dangerous, and it turns out not to be so, there's usually little consequence. However, if you claim something is not risky and it turns out to cause harm, the repercussions can be catastrophic. This can lead groups to be overly conservative in protecting their own interests. Looked at in this light, the Swiss Statement is remarkable.

Raise new research questions.

Much new data need to be uncovered to more fully answer the concerns raised by the community. How do STIs play a role in transmission and at what level? Do different strains of HIV affect its transmission? Do different classes of HIV drugs affect the levels of HIV in genital secretions differently? How do viral load blips affect transmission? How much do we know about HIV transmission through oral, vaginal or anal sex? Pursuing these and other questions are critical to help better inform those faced with these decisions.

Check out some of Project Inform's most recently updated publications, available at www.projectinform.org:

Bloodwork: Two Common Tests to Use; Bone Health and HIV Disease; Flu Season and Living with HIV; Peripheral Neuropathy; Towards a Healthy Liver

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