

HCV/HIV Today

May 2008

Volume 9, Issue 3

HCV/HIV Today
acknowledges
and thanks their
corporate
sponsor:
Factor Support
Network
Pharmacy

Clinical Breakthrough: Living & Loving

Swiss study shows zero transmission from certain HIV-infected persons to sexual partners

On January 30, 2008 Switzerland's Federal Commission on AIDS announced that certain persons with HIV/AIDS who have been on effective anti-retroviral drugs do not pass on the virus, even when engaging in unprotected sex.

The Federal AIDS Commission was focused on so-called serodiscordant partners where one is HIV-positive and the other is HIV-negative. According to the Commission, the HIV-positive person must be on effective and regular anti-retroviral therapy for a minimum of 6 months, present undetectable HIV viral load in his/her blood, and must be free of other sexually transmitted diseases.

The report sparked controversy and debate across AIDS communities in Europe, the US and Africa where it was met with a mixture of hope and concern from people living with HIV/AIDS, especially for those in a relationship with an HIV-negative partner.

According to the co-author of the report, Dr. Bernard Hirschel, an HIV/AIDS specialist at University Hospital in Geneva, these findings come from four different studies:

1) A study in Spain from 1990 through 2003

looked at 393 serodiscordant heterosexual couples. In this study, there were no infections transmitted to partners of HIV-positive individuals on anti-retroviral therapy (ART) compared to a rate of transmission of 8.6% among the partners of untreated patients. 2) A Ugandan study which followed a large cohort over a number of years, looked at viral loads in blood/plasma in untreated patients in serodiscordant partnerships, arrived at similar conclusions. 3) A Brazilian study of 92 serodiscordant couples found that in 41 cases in which the HIV-positive partner had started therapy, only six individuals were infected and all these occurred in partners of untreated patients with a viral load greater than 1,000 copies/ml. 4) A study of pregnant women concluded that perinatal transmission also is dependent on the maternal viral load and can be avoided by effective anti-retroviral therapy.

Roger Peabody of the Terrence Higgins AIDS Trust in London stated that, "the real thing missing here is about anal sex and acquiring a new sexually transmitted infection". Sexually transmitted infections, such as Chlamydia, or syphilis can increase the potential of HIV transmission in serodiscordant couples. Peabody added that, "We don't feel the scientific evidence is conclusive and there are some key issues that are not covered in the Swiss statement."

(Continued on page 8)

Inside Today

	Page
Note to Readers	2
Liver International	2
Researchers Uncover Clues to How HIV Promotes HCV Replication	3
Coverage of CROI 2008 (Conference on Retroviruses & Opportunistic Infections)	4-8
The Cure: Why, whether, how and when	9-12
AASLD 2007—Part 2: More Drugs in Development	13-15
Adjustment of Treatment Duration Based on Early Response	16

Note to the Reader: Unnecessary Liver Transplants?

One of our technical reviewers informed us, "I provide below the site for a recent, important, and very relevant investigative article:"

http://pittsburghlive.com/x/pittsburghtrib/news/s_556350.html

The internet site was for a Pittsburgh Tribune-Review three-part investigative series on unnecessary liver transplants that ran March 9-11, 2008. The reporters are Luis Fabregas and Andrew Conte, and can be reached at lfabregas@tribweb.com 412-320-7998 or andrewconte@tribweb.com 412-320-7835.

The first article stated, in part:

- "Hundreds of patients each year undergo liver transplants when they don't need them and possibly never will, a four month Pittsburgh Tribune-Review found."

The last article made the following points:

- "Transplants among least ill patients means big money for medical centers facing increased competition."
- "Liver transplant programs sometimes bypass the sickest patients because their reduced survival odds can hurt overall center success rates."
- "Of the 16,000 people on the national liver transplant waiting list, only about 3,400 are so sick that having a transplant would increase their odds of surviving."

Note to the Reader: One of our technical reviewers informed us, "Here's an interesting abstract." (See below) He went on to say the following: "Not ready for general use. Still it's an indicator that there's hope on the horizon."

Liver International

Volume 28, Issue 3, Page 347-354, March 2008

Abstract

All-trans retinoic acid for treatment of chronic hepatitis c

By Wulf O. Bocher ¹, Christian Wallasch ², Thomas Hohler ³, Peter R. Galle ¹

1. I Department of Internal Medicine, Johannes Gutenberg University Hospital, Mainz, Germany
2. GPC Biotech (former AXXIMA Biotech), Munchen, Germany
3. Department of Internal Medicine, Prosper Hospital, Recklinghausen, Germany

Correspondence:

Wulf O. Bocher, MD, I Department of Internal Medicine, Johannes Gutenberg University Hospital, Langebeckstrasse 1, 55131 Mainz, Germany

Tel: +49 6131 172666

Fax: +49 6131 176621

e-mail: boecher@mail.uni-mainz.de

Background/Aims: *In vitro* studies in the subgenomic hepatitis c virus (HCV) replicon system have identified all-trans retinoic acid (ATRA) as a potential therapeutic against hepatitis c. Thus, the antiviral potential of this drug should be assessed *in vivo*.

Methods: Twenty highly treatment experienced serotype 1 patients with non-response to conventional or pegylated interferon-a (Peg-IFN-a) and ribavirin were randomly assigned to 12 weeks of monotherapy with ATRA (group A) or a combination of ATRA and PegIFN-a2a (group B). HCV RNA was assessed by bDNA assay and if negative by highly sensitive

(Continued on page 8)

HCV/HIV Today is published bi-monthly by the Hemophilia Association of the Capital Area. Comments and questions from our readers are strongly encouraged. Please address all correspondence to Editor: HACA, 10560 Main Street, Suite 604, Fairfax, VA 22030 or call (703) 352-7641. Any information contained in this newsletter related to the diagnosis or treatment of either hemophilia, HIV or HCV is intended for educational purposes only; HACA does not recommend or discourage any specific medical services or treatments. All questions regarding medical care should be decided by patients in consultation with their physicians or medical providers. Any reader wishing to learn more about any topic contained in this newsletter can contact HACA, and will be directed to the appropriate source.

Researchers Uncover Clues to How HIV Promotes Hepatitis C Virus Replication

By Liz Highleyman

Considerable research indicates that HIV positive individuals coinfecting with hepatitis C virus (HCV) tend to experience more rapid liver disease progression and respond less well to interferon-based hepatitis C treatment than HIV negative people with HCV alone.

In a laboratory study described in the March 2008 issue of *Gastroenterology*, researchers at Massachusetts General Hospital and Harvard Medical School shed light on a potential mechanism underlying this phenomenon. As background, the authors noted that it has so far been unclear how HIV -- which does not target hepatocytes -- is able to accelerate liver disease progression in people with HCV.

In the present analysis, the investigators assessed whether circulating HIV or specific HIV proteins might contribute to HCV pathogenesis through engagement of co-receptors on hepatocytes.

Results

Inactivated HIV and the HIV gp120 envelope glycoprotein were associated with increased HCV replication in both a replicon and an infectious model of hepatitis C.

HCV-regulated transforming growth factor-beta-1 (TGF-beta-1) expression was enhanced in the presence of HIV and gp120.

Conversely, TGF-beta-1 also enhanced HCV replication.

The promoter effect of HIV and gp120 on HCV replication was neutralized by antibodies to the CCR5 or CXCR4 co-receptors, which HIV uses to enter cells.

HIV and gp120 did not alter type I interferon-mediated signaling in these HCV models, indicating that HIV regulates HCV replication through an alternative mechanism.

The effect of HIV on HCV replication was blocked by a neutralizing antibody to TGF-beta-1, indicating that the promoter effect is TGF-beta-1 dependent.

Conclusion

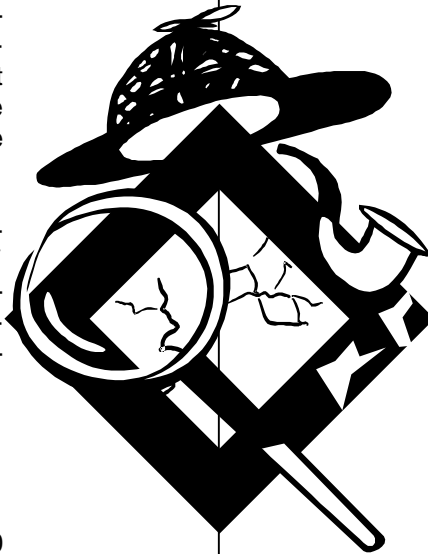
In conclusion, the investigators wrote, "These results suggest a novel mechanism by which HIV not only enhances HCV replication but also contributes to progression of hepatic fibrosis."

Related research presented at the 15th Conference on Retroviruses and Opportunistic Infections (CROI 2008) last month in Boston indicated that HIV can infect hepatic stellate cells, a type of support cell in the liver that produces scar tissue, which also appears to contribute to accelerated fibrosis progression in coinfecting individuals.

Reference

W Lin, EM Weinberg, AW Tai, and others. HIV Increases HCV Replication in a TGF-beta1-Dependent Manner. *Gastroenterology* 134(3): 803-811. March 2008.

HIVandHepatitis.com, March 14, 2008



Coverage of CROI 2008 (Conference on Retroviruses and Opportunistic Infections) February 4–6, 2008, Boston, MA

Viramune: maybe twice a day, maybe once a day

February 5, 2008

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

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

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

Best use of Selzentry still in question

February 5, 2008

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

As reported here, the first set of results from the MERIT study were presented at the 2007 IAS meeting. MERIT compared Selzentry to Sustiva (efavirenz) both taken

with the NRTI fixed-dose combination Truvada (Viread/tenofovir + Emtriva/emtricitabine) in people taking HIV drugs for the first time. Overall, Selzentry didn't quite match up to Sustiva. Surprisingly, the difference between the drugs was only seen in people in the southern hemisphere.

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

These results raise more questions about using Selzentry in people taking HIV drugs for the first time. One issue is the reliability of the Trofile test—the only widely used test that tells whether a person's HIV is only R5 or can use X4. A small but significant group of people had different results in the short time between screening and taking their first dose. This issue is important because it takes 3 or more weeks to get the results of the Trofile test back.

However, the biggest problem is the higher rates of treatment failure compared to Sustiva, which is widely used as first line treatment. While it's true that more people stopped taking Sustiva due to intolerance in this study, the treatment failures from people who took Selzentry often led them to develop resistance to other drugs in their regimens. This, in turn, limits their future treatment options.

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

high pre-treatment HIV levels, only around 35% had undetectable HIV levels compared to almost 60% of people with lower pre-treatment levels.

There were no significant differences in rates of side effects between these two groups. This is important to emphasize, because there has been a high degree of concern over toxicity with this class of drugs. So far, these concerns haven't been confirmed with Selzentry.

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

SMART study reports on re-starting ART

February 4, 2008

In what might be the final large presentation from the landmark SMART study, researchers reported that people who re-started HIV treatment on the recommendation of the study experienced significant immune recovery and improved survival. Today's CROI presentation showed that participants in the intermittent treatment group of SMART who chose to re-start treatment gained most, but not all, of the benefits experienced by people in the continuous group. This marks another important chapter in the strange odyssey of SMART.

SMART was the largest randomized, prospective trial ever done in HIV. It compared two treatment strategies: CD4 guided intermittent treatment (*drug conservation* or DC group) vs. continuous treatment (*viral suppression* or VS group). As widely reported, enrolling in SMART was stopped early, and the study was altered when an early look at the data showed much higher rates of opportunistic and non-opportunistic diseases and death for people in the DC group. After enrollment was stopped, all the participants were informed of the results. Anyone in the DC group who had stopped taking HIV drugs was recommended to start HIV drugs.

The study presented today at CROI looked at this group. The combined risk of opportunistic diseases and death dropped by about half (from 3.4 to 1.9 per 100 person years). This risk remained somewhat higher than in the VS group, at 1.4 per 100 person years. Similar reductions were seen in rates of cardiovascular disease,

where the incidence went from 1.8 to 1.1 in the DC group, still above the 0.9 in the VS group.

People who chose to re-start HIV drugs in the DC group also showed higher CD4 counts, but they remained below the levels at the start of the study. This confirms results from other treatment interruption studies showing that immune recovery is slower after interrupting treatment compared to starting treatment.

The designers of the SMART study had hypothesized that by reducing the amount of time that a person was exposed to HIV drugs, they would likely have lower rates of heart disease and other problems thought to be linked to the drugs. The results showed just the opposite and made many question the wisdom of treatment interruptions. It also highlighted the growing understanding of the damage that untreated HIV does to the body.

CASTLE study compares Reyataz to Kaletra

February 4, 2008

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

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

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

This study confirms the growing body of evidence that most, though not all, boosted protease inhibitor regimens perform about the same in lowering HIV levels

(Continued on page 6)

(Continued from page 5)

and raising CD4 counts. The most important differences are found in side effects, drug interactions and convenience. While Kaletra enjoyed a period alone at the top of the pile, the field is now quite crowded, which is a good thing for people with HIV who now have more choices for boosted protease inhibitor regimens than ever before.

HEAT study shows Epzicom as good as Truvada when paired with Kaletra

February 4, 2008

A poster presented today found that the widely used fixed-dose combination pills, Epzicom (Ziagen/abacavir + Epivir/lamivudine) and Truvada (Viread/tenofovir + Emtriva/emtricitibine), performed equally well when they're taken with the boosted protease inhibitor, Kaletra (lopinavir + ritonavir). This head-to-head study, called HEAT, is important because there isn't much direct comparison data between Epzicom and Truvada, which are the two preferred fixed-dose combination NRTI pills found in the current federal guidelines.

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

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

The current federal guidelines, released in late January, list both Truvada and Epzicom as the preferred options for first line treatment. To date, there has been little direct comparison data to help people choose between these two options. The results from HEAT suggest that either of them is likely to work well, at least when taken with once daily Kaletra.

There are a couple of secondary but important notes about this study. First, it used Kaletra once a day rather than the more widely used and better supported

twice a day schedule. This might explain the higher levels of resistance to NRTIs than is typically seen in clinical studies. Also, HLA testing—which fairly accurately predicts the risk of having an abacavir HSR—was not used in the study. Other studies, like PREDICT and SHAPE, suggest that if HLA testing had been used, then a much lower rate of abacavir HSR would likely have occurred.

The other important note is that this study only compared these combination pills when taken with Kaletra. While Kaletra is widely used in first line therapy, others—notably Sustiva (efavirenz) and Reyataz (atazanavir)—are also common choices for first line therapy. It would be a mistake to interpret these results to mean that other drug combinations are less effective than the two used in HEAT.

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

Stem cells: Progress towards “the cure”?

February 12, 2008

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

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

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

Research shows that people who lack this receptor are highly resistant to HIV infection. We inherit two copies of the gene that makes this receptor, one from each of our parents. If a copy from one parent is defective, a person generally becomes a slow progres-

sor if infected by HIV because of the lower number of functional CCR5 receptors. If copies from both parents are defective, a person is highly resistant to HIV infection or, if infected, typically becomes a long-term non-progressor.

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

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

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

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

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

This is another one of the kind of "one step at a time"

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

Experimental NtRTI may cause fewer kidney problems

February 5, 2008

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

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

Gilead also looked at how well GS-9148 got into lymph node cells. Lymph nodes are a major site of HIV replication. Most HIV drugs fail to penetrate into this important area of the immune system.

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

Apricitabine shows some promise

February 5, 2008

A poster presented at CROI shows potential for the experimental NRTI, apricitabine. The results came from the AVX-201 study, which Project Inform reported about earlier. AVX-201 compared apricitabine to Efavir (lamivudine) in people with HIV that harbors the M184V mutation, which is associated with resistance to Efavir and Emtriva (emtricitabine).

In the first phase of the study, people on failing Efavir regimens were randomly assigned to either stay on Efavir or switch to apricitabine. After 21 days every

(Continued on page 8)

(Continued from page 1)

Clinical Breakthrough: Living & Loving (continued)

The National AIDS Council of France warned that “the findings were not robust enough to extrapolate wider conclusions from the individual cases cited.”

However, Dr. Hirschel stated that, “I know these conclusions can provoke certain fears, but I think such credible information which relies on proven and certain facts should be made known.”

In our community, the HIV infected and affected have reacted with hope and some concern regarding the advice of the Swiss Federal Commission on AIDS. COTT’s core constituency includes many serodiscordant couple who continue to struggle with issues relating to the boundaries of safe sex and what is appropriate and desirable for the protection of an HIV-negative partner.

One concern about the Swiss recommendations is that there are reports that some people with undetectable viral load in blood/plasma have had measurable

viral load in seminal fluid. However, “the only data we have correlating viral load with transmission is the blood/plasma viral load”, according to Dr. Rich Colvin of the Infectious Diseases Unit at Massachusetts General Hospital, a longtime member of COTT’s Board of Directors.

COTT President, Corey Dubin stated that, “We have always supported living and loving for people with HIV disease and these conclusions certainly contribute to de-stigmatizing sexuality and HIV infection”. Adding that, “the boundaries of safe sex are a decision to be made ultimately in open discussion between serodiscordant partners with the best medical information to support open and honest dialogue.”

For COTT, part of what is interesting here is that practicing AIDS doctors are communicating these conclusions energetically; historically it has been the activist community that has strongly stated their belief that data would eventually lead to these conclusions, and as a result would be a necessary part of de-stigmatizing HIV infection and the people living with HIV/AIDS.

Cott’s Dateline, February 2008

(Continued from page 2)

Liver International (continued)

polymerase chain reaction.

Results: During treatment, five of 10 patients in group A had a drop of viraemia >1log, while in group B after 8 weeks five of 10 dropped >2log, and three of 10 cleared HCV RNA from serum. Viraemia relapsed after treatment cessation. ATRA was rather well tolerated, with transient headache, dry skin and mucosa representing the most common side effects.

Conclusions: The viral load reduction under ATRA monotherapy, although limited and transient, supports the antiviral activity of ATRA. However, the rapid loss of HCV RNA in three of 10 previous non-responder under ATRA and PegIFN-a2a treatment demonstrates a strong additive or synergistic ATRA effect and calls for a controlled trial to assess the therapeutic potential of this drug.

(Continued from page 7)

Coverage of CROI 2008 (continued)

one was switched to a background regimen made up of the best available HIV drugs. Results from this second phase were presented at CROI.

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

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

Project Inform, February 2008

The Cure: Why, whether, how and when

by Martin Delaney

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

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

1. Why is a cure so important?

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

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

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

Another thing typically overlooked is the lifetime cost of treatment which currently averages between \$12,000–\$25,000 a year for relatively healthy people with HIV,

and much more for those in advanced stages of disease. While these costs have been met in the short-term, we’re only beginning to look at the lifetime costs of being on regimens for up to 50 years. It’s simple: do the math!

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

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

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

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

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

(Continued on page 10)

(Continued from page 9)

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

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

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

2. Is a cure feasible?

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

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

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

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

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

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

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

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

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

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

3. How can HIV be cured?

It is admittedly premature to pronounce that one approach or another is the most likely avenue to curing HIV. Instead, there are a number of possibilities. What we need are some serious programs to develop and

(Continued on page 11)

test them. So far, the most widely tested approach has used just antivirals, alone or together with another kind of drug to try to eradicate HIV.

Scientists back in 1996 thought it would be enough to simply give people the strongest antivirals for several years in a row and this would gradually eliminate even the last copies of HIV. They were wrong, but this led to the discovery that HIV was being sustained, in relatively small amounts, in “reservoirs.” These were generally inactive cells, like memory T-cells, which the immune system only rarely activates and uses. They’re largely unaffected by HIV drugs and the immune system. For some reason they can only be reached when they are activated.

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

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

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

A recently reported case study from Germany described what happened when a patient was given a stem cell transplant, for treating cancer, by using cells from a donor who lacked the genes that cause the body to make the CCR5 receptor favored by HIV. This case study is described in more detail on Project Inform’s website in our coverage of CROI 2008.

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

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

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

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

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

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

4. When can a cure happen?

This question is impossible to answer. At best, prediction is a tricky business. However, a number of the more enthusiastic researchers seeking a cure believe that the solution may be closer than most believe. Claims that it won’t be possible until far in to the future are based on

(Continued on page 12)

(Continued from page 11)

the false definition of cure, the one that demands absolute eradication. Once we realize that this is not required, the cure doesn't seem so very far away.

It's now routine to reach HIV levels below 50 copies [per ml]. Studies with new drugs are now using a test that measures down to 5 or 10 copies, and there's evidence that the drugs are succeeding at this level. Researchers will need to retest various eradication approaches using these new therapies. We really don't know what happens when HIV is suppressed this low for long periods. Similarly, a few first generation gene therapy studies are well underway and near completion. These may not be the total solution but could well point us there, as does the German stem cell transplant program. The most optimistic researchers we have spoken to believe we will see the first evidence of a cure in as soon as 5-10 years.

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

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

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

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

as well as clinical research.

Efforts are underway to make this happen. In Dec. 2007, more than 125 scientists from around the world came together in a meeting dedicated to unraveling the challenge of HIV persistence and eradication. These scientists, along with a few activists and foundation representatives, are committed to this type of research.

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

Collectively, we hope to further influence the Division of AIDS at the National Institute of Allergy and Infectious Diseases to increase its commitment to this type of research.

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

A personal comment

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

Project Inform, PI Perspective #45, April 2008

AASLD 2007 – Part 2: More Drugs in Development

Alan Franciscus, Editor-in-Chief

In part two of a report from the American Association for the Study of Liver Diseases (AASLD) Conference on drugs in development I will further review information presented at AASLD 2007. I will also continue to add my thoughts about these new drugs. However, keep in mind that most of the drugs discussed in this article are in very early development and that it is particularly difficult to evaluate whether these drugs will be viable treatment options until there have been more studies with a larger patient population. The drugs I will concentrate in this article are **nitazoxanide**, **R7128**, **Bavituximab**, **GS-9190**, and **VCH-759**.

Nitazoxanide

Nitazoxanide (brand name Alinia – Romark Laboratories) is a broad spectrum antiviral drug that is approved by the Food and Drug Administration (FDA) for treating diarrhea caused by *Giardia* and cryptosporidium (protozoan pathogens that infect the GI tract). In previous studies nitazoxanide was found to be safe and well-tolerated and showed antiviral activity against the hepatitis C virus. It was also found in the earlier studies that the combination of nitazoxanide and interferon produced a synergistic effect (the sum of the combination creates a greater effect than the use of the agents separately). At AASLD the results from one study named STEALTH C-1 were presented. STEALTH C is – **STudies to Evaluate Alinia for Treatment of Hepatitis C**. The study was conducted in Egypt among genotype 4 patients.

There were three treatment groups in the study:

Group A: Nitazoxanide in dual therapy with Pegasys

28 treatment naïve and 12 interferon experienced patients – treatment duration 36 weeks (included a 12 week lead-in phase of nitazoxanide only)

Group B: Nitazoxanide in triple therapy with Pegasys plus ribavirin

28 treatment naïve patients and 12 interferon experienced patients – treatment duration 36 weeks (included a 12 week lead-in phase of nitazoxanide only)

Group C: Standard of care (control) with Pegasys plus ribavirin

40 treatment naïve patients– treatment duration 48 weeks

The medications: nitazoxanide (500 mg pill twice a day), Pegasys 180 ug injection weekly, and ribavirin

pill 1000/1200 daily (weight based).

All patients received a liver biopsy at baseline, and the weekly injections of Pegasys were given at the clinic. HCV RNA, lab work and a physical exam were conducted every 4 weeks. Baseline characteristics of the trial participants were well matched across treatment groups. **Note:** Groups A & B had a 12 week lead-in phase of nitazoxanide treatment that produced a modest, but statistically significant drop in HCV RNA. In an intention-to-treat analysis (all patients who received one dose counted) SVR (undetectable HCV RNA (<10 IU/mL) 12 weeks post treatment) results were 68% in the naïve patients in group A (dual therapy), 79% in group B (triple therapy) and 43% in group C (control). It was also pointed out that in the patients who received nitazoxanide none of the patients relapsed (return of HCV RNA) compared to 15% of patients who relapsed in the control group that **did not** receive nitazoxanide. There were no treatment discontinuations due to adverse events in the nitazoxanide treatment groups directly related to the drug.

In the **interferon experienced** treatment arms of the study, SVR 12 week results were 8% in group A (dual therapy) and 25% in group B (triple therapy). It was pointed out that the small numbers of interferon experienced patients in the study made it difficult to draw any concrete conclusions about the effectiveness of nitazoxanide containing regimes for retreatment.

Bottom line: This study is very interesting because it seems (at least in the early stage) that there is a substantial benefit when nitazoxanide is added to pegylated interferon plus ribavirin therapy. There is also a possibility that adding nitazoxanide could possibly lead to a shorter duration of treatment. However, a bit of caution is needed. Most importantly all of the patients were HCV genotype 4 who, typically, as a group, achieve a higher response rate compared to people with genotype 1. In addition, the data presented was the 12 week SVR results so the results 24 weeks post-treatment (SVR 24) are needed to confirm whether these truly represent SVR. A larger trial of genotype 4 treatment non-responders (STEALTH C-2) is ongoing and will give a better picture of the effectiveness of adding nitazoxanide to pegylated interferon plus ribavirin in the treatment of non-responders, who are typically a very difficult group to retreat.

The next step in the development process is a planned

(Continued on page 14)

(Continued from page 13)

clinical trial to be named STEALTH C-3 that will be conducted in HCV genotype 1 treatment naïve patients. In this study there will be 4 groups (80 patients in each treatment arm). The study arms will have a 4 week lead-in phase of nitazoxanide only (except in the placebo group) with an additional treatment duration of 48 weeks with various combinations of nitazoxanide, Pegasys, and ribavirin. In one arm, patients who achieve a rapid virological response (HCV negative after 4 weeks of triple combination) will only be treated for 24 weeks. This study will test the safety, tolerability, and effectiveness of the combination of drugs as well as look at the effect of shortening treatment duration and will study the effectiveness of combining nitazoxanide plus Pegasys without ribavirin. This will definitely be one of the most interesting studies to follow in 2008-2009.

R7128

R7128 is an HCV polymerase Inhibitor that is being developed by Pharmasset and Roche. In this study there were 40 HCV Genotype 1 patients who were previously treated (but non-responders or relapsers) with interferon or interferon plus ribavirin therapy. There were 5 treatment groups (8 patients in each group) with various doses of R7128 (750 mg QD, 1500 mg QD, 750 mg BID, 1500 mg BID) or placebo. (Note: QD=once a day; BID=twice a day.)

The baseline characteristics of the participants were well matched across the treatment arms. R7128 demonstrated dose-dependent decreases in HCV RNA through the 14 days of monotherapy treatment in all the patients who received R7128 with a mean 2.7 log₁₀ decline of HCV RNA and a maximum decline of 4.2 log₁₀. It was found that twice a day dosing was superior to once a day dosing. In the participants who were treated with R7128 who had abnormal ALT levels, 78% of the participants' ALT levels normalized. R7128 was generally well-tolerated.

Bottom line: It is too early to tell if this drug will be a viable drug for treating hepatitis C, but if the twice a day dose proves to be effective it will be an improvement over the three or four times a day dosing of some of the other drugs in development.

Bavituximab

Bavituximab is an anti-phosphotidylserine monoclonal antibody immunotherapeutic that is being investigated to treat hepatitis C. At AASLD the results from a phase 1b study of 24 patients (15 males, mean age 49) were presented. In the study, 11 of the patients were treatment non-responders, 8 were treatment relapsers and 5 were

treatment-naïve. The mean baseline HCV RNA was 5,000,000 copies/mL. Fifteen patients were infected with HCV genotype 1, 8 patients were infected with genotype 3, and 1 patient was infected with genotype 2. Bavituximab was given by infusions for two weeks at doses of 0.3, 1, 3 or 6 mg/kg. The patients were observed for a total of 12 weeks. All of the patients in all the dosing groups achieved a greater than or equal to 0.5 log₁₀ reduction in HCV RNA. In the 3 mg/kg group 83% of the patients had viral load reductions, and this is the dose that Peregrine will advance into future clinical studies. The infusions were well-tolerated with no serious adverse events or early discontinuations reported. There was one grade 3 neck pain and arthralgia (joint pain) in a study participant with a history of joint pain (in the 3 mg/kg group) that was considered dose-related to the study drug.

Bottom line: Given the modest antiviral properties of bavituximab it will be interesting to see if there will be a synergistic effect when combined with interferon/ribavirin therapy. This could mean an improvement in treatment outcome over the current standard of care.

GS-9190

GS-9190 is an HCV non-nucleoside polymerase inhibitor that is being developed by Gilead Sciences. The results from a phase I study (part A & part B) were presented at AASLD.

Part A: 31 HCV genotype 1 treatment naïve patients were treated with escalating doses of GS-9190 (40 mg, 120 mg, 240 mg, 480 mg, and 240 mg with food) or placebo. The mean age of the study participants was 44 yo; they were mostly white males and had a median HCV RNA of 6.56 log₁₀. The HCV RNA reductions seen in a single dose of GS-9190 (across all doses) ranged from 0.7 to 1.2 log₁₀. GS-9190 was well-tolerated with no serious treatment-limiting adverse events.

Part B: Based on the results from Part A, Part B was initiated to study multiple doses of GS-9190 in 23 trial participants over an eight day period. The study participants received one of the following doses – 40 mg BID, 120 mg BID, 240 mg QD or 240 mg BID. The baseline mean HCV RNA was 6.65 log₁₀ and the mean age was 44 yo. The participants were mostly white males. Data from the 240 mg QD and 240 mg BID groups was available and presented at AASLD.

The reduction in HCV RNA was 1.4 log₁₀ for the 40 mg group and 1.710 for the 120 mg BID group. GS-9190 given twice daily over the eight day period was generally well-tolerated. Included in the study design was an electrocardiographic assessment to test for any potential

defects in heart rhythm. In Part B a possible case of QT (arrhythmia) was noted. Based on this finding, Gilead has initiated a study in healthy subjects to further evaluate the effect of GS-9190 on the heart. The results from the QT study are expected to be available by the end of 2007.

Bottom line: Again too early to tell if this is going to be an effective drug to treat HCV, but if it is found that there is no relationship between GS-9190 and QT, Gilead will continue to study the drug as a possible treatment for hepatitis C. Results from the QT study in healthy adults are expected to be released by the end of 2007.

VCH-759

VCH-759 is an HCV non-nucleoside polymerase inhibitor. The results of a phase I study of 32 HCV treatment naïve patients (31 patients with genotype 1, 1 patient with genotype 6) were released at AASLD. It was noted that the results of the effectiveness of VCH-759 in the person with genotype 6 were not included in the final results. However, the side effect and safety information from the genotype 6 patient was included in the overall

safety information.

The participants were randomized into 4 treatment arms:

- 400 mg TID (three times a day) – 8 patients
- 800 mg BID – 5 patients
- 800 mg TID – 9 patients
- Placebo – 9 patients (included in all treatment arms)

The results showed that all the patients who received VCH-759 achieved more than a 1 log₁₀ decrease in HCV RNA. The 800 mg TID group had the highest log decrease – 2.5 log₁₀. The drug was well-tolerated over 10 days. Studies are underway to determine if there are any mutations associated with viral rebound in some of the subjects who relapsed before the final dose of VCH-759 was given.

Bottom line: This information is very early data and there can be no conclusions made about the future development of this drug. However, the results of the genetic sequencing will give a better indication of the drug resistance and whether or not this drug will be advanced into larger studies.

HCV Advocate, January 2008

(Continued from page 17)

In the future, the best hope for shortening hepatitis C treatment may come from targeted antiviral agents. For example, interim data from the PROVE 1 trial, looking at the HCV protease inhibitor telaprevir plus Pegasys with or without 1000-1200 mg/day ribavirin, showed that 61% of genotype 1 patients receiving the triple combination achieved SVR after 24 weeks of therapy—higher than the sustained response rate with pegylated interferon/ribavirin for 48 weeks in most studies.

References

- Dalgard, O. et al. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. *Hepatology* 47(1): 35-42. January 2008.
- Kamal, S.M. et al. Pegylated interferon alpha-2b plus ribavirin in patients with genotype 4 chronic hepatitis C: The role of rapid and early virologic response. *Hepatology* 46(6):1732-40. December 2007.
- Jacobson, I.M. et al. Interim analysis results from a Phase 2 study of telaprevir with peginterferon alfa-2A and ribavirin in treatment-naïve subjects with hepatitis C. 58th AASLD. Boston. November 2-6, 2007. Abstract 177.
- Mangia, A. et al. Individualized treatment duration for hepatitis C genotype 1 patients: A randomized controlled trial. *Hepatology* 47(1): 43-50. January 2008.
- Marcellin, P. et al. Which patients with genotype 1 chronic hepatitis C can benefit from prolonged treatment with the 'accordion' regimen? *Journal of Hepatology* 47(4): 580-587. October 2007.
- Martin-Carbonero, L. et al. Undetectable hepatitis C virus RNA at week 4 as predictor of sustained virological response in HIV patients with chronic hepatitis C. *AIDS* 22(1): 15-21, January 2, 2008.
- McMahon, J. et al. Efficacy of a 72-week course of treatment for previous relapsers to PEG/ribavirin therapy. Digestive Disease Week 2007. Washington, DC. May 19-24, 2007. Abstract S1232.
- Pearlman, B.L. et al. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis C genotype 1-infected slow responders. *Hepatology* 46(6): 1688-1694. December 2007.
- Pianko, S. et al. Ultra rapid virologic response predicts sustained virologic response in HCV infected patients with genotype 3 and high viral load: the Get-C Study. 58th AASLD. Boston. November 2-6, 2007. Abstract 349.
- Poordad, F. et al. Rapid virologic response: a new milestone in the management of chronic hepatitis C. *Clinical Infectious Diseases* 46(1): 78-84. January 1, 2008.
- Shiffman, M.L. et al Peginterferon Alfa-2a and Ribavirin for 16 or 24 Weeks in HCV Genotype 2 or 3. *New England Journal of Medicine* 357(2): 124-134. July 12, 2007.

HCV Advocate, February 2008

Adjustment of Treatment Duration Based on Early Response

Liz Highleyman

Pegylated interferon (Pegasys or PegIntron) plus weight-based ribavirin for 24 weeks (HCV genotypes 2 and 3) or 48 weeks (genotype 1) is the standard of care for treating chronic hepatitis C. But a growing body of research suggests that less standardization may be better.

Standard treatment, determined via large clinical trials, represents the best overall regimen for the population as a whole, but may not be optimal for a specific individual. Given the difficult side effects and expense of interferon-based therapy, patients and their clinicians would prefer treatment that lasts just long enough to cure hepatitis C – no more and no less.

Several recent studies have shown that some “fast responder” patients can achieve sustained virological response (SVR) with a shorter than usual duration of therapy, while “slow responders” may need longer treatment. The speed with which viral load declines during early treatment is a major predictor of how long treatment should last.

Treatment Duration Based on Initial Response

In a study described in the January 2008 issue of *Hepatology*, Alessandra Mangia and colleagues explored whether a shorter duration of therapy might be sufficient for genotype 1 patients who experience rapid virological response (RVR), or undetectable viral load at Week 4. Nearly 700 participants were treated with standard doses of Pegasys or PegIntron plus 1000-1200 mg/day weight-based ribavirin. One group was randomly assigned to receive treatment for the standard 48-week duration, while the others were treated for 24, 48, or 72 weeks, depending on whether their viral load first became undetectable at Week 4, Week 8, or Week 72, respectively.

Similar proportions first achieved undetectable viral load at Week 4 (27%) and at Week 8 (28%), with a further 11% having cleared HCV at Week 12. Overall, 45% in the standard duration arm and 49% in the variable duration arm achieved SVR. Among patients who first achieved undetectable HCV RNA at Week 4, 87% in the standard duration arm and 77% in the variable duration (24-week) arm achieved SVR. However, the subset of patients in this group who had a high baseline viral load did better with 48-week than 24-week treatment (SVR 87% vs 73%). Among individuals who achieved undetectable HCV RNA at Week 8, SVR rates were similar in the standard and variable duration

(48-week) arms (70% vs 72%). But among the slowest responders at Week 12, the SVR rates were 38% in the standard duration arm and 64% in the variable duration (72-week) arm, demonstrating a benefit from longer treatment.

Though less well studied, even earlier HCV clearance may predict ultimate treatment outcomes. In the ongoing GET-C study, looking at extended therapy for genotype 3 patients with a high baseline viral load, ultra-rapid virological response at Week 2 predicted SVR with 93% accuracy.

Response to hepatitis C treatment is described based on the amount of HCV RNA, or viral load, at different points in time:

- **Ultra-rapid virological response (URVR):** undetectable HCV RNA at Week 2 of treatment.
- **Rapid virological response (RVR):** undetectable HCV RNA at Week 4 of treatment.
- **Early virological response (EVR):** traditionally, at least a 2-log drop in HCV RNA at Week 12 of treatment (though some researchers use undetectable viral load).
- **End-of-treatment response (EOT or ETR):** undetectable HCV RNA at the completion of treatment (typically Week 24 for genotypes 2 or 3; Week 48 for genotype 1).
- **Sustained virological response (SVR):** continued undetectable viral load 24 weeks after the completion of therapy (typically Week 48 for genotypes 2 or 3; Week 72 for genotype 1).

Longer Treatment for Genotype 1

As reported in the December 2007 issue of *Hepatology*, Brian Pearlman and colleagues specifically assessed whether longer treatment would produce a greater likelihood of SVR in previously untreated genotype 1 patients classified as “slow responders,” defined as having at least a 2-log reduction but still detectable HCV RNA at Week 12, but undetectable viral load at Week 24.

About 100 study participants were randomly assigned to receive PegIntron plus 800-1400 mg/day weight-based ribavirin for either the standard 48 weeks or an extended 72 weeks. End-of-treatment response rates were similar in the 48-week and 72-week arms, at 45% vs 48%, respectively. However,

HCV relapse occurred less often with longer treatment, thus yielding a higher SVR rate (18% vs 38%). Despite longer therapy, the frequency of dose reductions and treatment discontinuation due to side effects were similar in both groups.

Longer treatment may also lead to sustained response in prior relapsers. As reported at the Digestive Disease Week 2007 conference, Jeffrey McMahon and colleagues assessed 72-week treatment with Pegasys plus ribavirin in four patients (three with genotype 1 and one with genotype 2) who relapsed after a previous 48-week course of combination therapy. During re-treatment, all experienced HCV clearance by Week 12 and achieved SVR.

Other HCV Genotypes

Tailored treatment durations may also benefit patients with other HCV genotypes. Studies have suggested that treatment shorter than the standard 24 weeks can produce sustained response in many genotype 2 and 3 patients, but the longer regimen appears to be superior overall.

In the July 12, 2007 *New England Journal of Medicine*, for example, Mitchell Shiffman and colleagues reported results from the ACCELERATE trial, in which 1,469 genotype 2 or 3 patients were randomly assigned to receive Pegasys plus 800 mg ribavirin for either 16 or 24 weeks. The overall SVR rates were 62% in the 16-week group and 70% in the 24-week group, and the relapse rate was significantly higher in the shorter treatment arm (31% vs 18%). However, among participants who achieved RVR at Week 4, the SVR rates were 79% and 85%, respectively. And among those with a low baseline viral load, SVR rates were similar in both treatment arms (82% vs 81%). The researchers concluded that "16 weeks may be adequate for a carefully selected subset of patients."

Similarly, in the January 2008 issue of *Hepatology*, Olav Dalgard and colleagues reported that among 428 genotype 2 or 3 patients treated with PegIntron plus 800-1400 mg ribavirin who cleared HCV by Week 4, 81% achieved SVR with a 14-week course of treatment, compared with 91% of those treated for 24 weeks, which did not meet the non-inferiority criteria. "However," they wrote, "the SVR rate after 14 weeks of treatment is high, and although longer treatment may give slightly better SVR, we believe economical savings and fewer side effects make it rational to treat patients with genotype 2 or 3 and RVR for only 14 weeks."

Finally, as reported in the December 2007 issue of *Hepatology*, Sanaa Kamal and colleagues treated 358 Egyptian genotype 4 patients with PegIntron plus

weight-based ribavirin for variable durations based on early response. Individuals with RVR at Week 4 were treated for 24 weeks, and 86% achieved SVR. This compared with 76% for patients with undetectable viral load at Week 12 treated for 36 weeks, and 56% for those with continued detectable HCV RNA at Week 12 treated for 48 weeks. In a control group, all participants were treated for 48 weeks regardless of early response, and 58% achieved SVR.

HIV/HCV Coinfection

Researchers have also explored variable treatment durations in HIV/HCV coinfecting individuals. HIV positive patients may clear HCV more slowly, leading some experts to suggest that they might benefit from longer treatment.

As reported in several recent conference abstracts and journal articles, the Spanish PRESCO trial included 389 coinfecting participants, about half with genotype 1, treated with Pegasys plus 1000-1200 mg/day ribavirin. Those who achieved early virological response at Week 12 were randomly assigned to continue treatment for either 48 or 72 weeks (genotype 1 or 4) or for either 24 or 48 weeks (genotype 2 or 3). Overall, 36% of genotype 1 patients, 72% with genotype 2 or 3, and 33% with genotype 4 achieved SVR. Undetectable HCV RNA at Week 4 was the best predictor of sustained response. Extended treatment duration did not appear to reduce the risk of relapse.

Treat Long Enough – But Not Too Long

HCV viral load at Week 4 is "emerging as an important milestone" in the management of chronic hepatitis C, according to Fred Poordad and colleagues. Based on a recent review of past research, they concluded that shortening treatment to 12-16 weeks is effective for genotype 2 or 3 patients who attain RVR; for genotype 1 patients, RVR may be used as an indicator for both shortened and extended treatment. RVR "represents a key opportunity to individualize therapy according to treatment-related viral kinetics," they wrote in the January 1, 2008 issue of *Clinical Infectious Diseases*.

But clinicians should not be too quick to alter the duration of hepatitis C treatment. Even among patients who achieve RVR at Week 4, some may experience relapse with a shortened course of therapy. Conversely, in the October 2007 *Journal of Hepatology*, Patrick Marcellin, Jenny Heathcote, and Antonio Craxi advised against "indiscriminate extension of treatment," since this can lead to prolonged side effects and higher cost for some patients who still will not achieve a cure. It remains a challenge, they wrote, to distinguishing at an early stage between "slow responders" and "null responders."

(Continued on page 15)

HACA - Today
10560 Main Street, Suite 604
Fairfax, VA 22030

Non-Profit Org.
Bulk Rate
U.S. Postage
PAID
Fairfax, VA
Permit No. 715

Obstacles cannot crush
me.
Every obstacle yields to
stern resolve.
He who is fixed to a star
does not change his
mind.

Leonardo da Vinci

